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PATENT
454312-2420

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#30
OM
10/4/02

Applicant(s)	:	Alan G. Barbour and Catherine J. Luke
U.S. Serial No.	:	08/588,637
For	:	COMPOSITIONS AND METHODS FOR ADMINISTERING BORRELIA BURGDORFERI ANTIGENS
Filed	:	January 19, 1996
Examiner	:	R. Swartz
Group Art Unit	:	1645

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New York, NY 10151

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REPLY BRIEF

Board of Patent Appeals and Interferences
Commissioner for Patents
Washington, D.C. 20231
Sir:

INTRODUCTION

This is an Appeal from the February 21, 2001 Final Rejection by the Examiner, and from the November 8, 2001 Advisory Action, finally rejecting claims 1-4, 6-10, 12 and 13, with an Appeal Brief having been filed in triplicate on February 20, 2002, and the Examiner's Answer having been mailed August 7, 2002. Oral argument has been requested.

This Brief is submitted in triplicate, and, the Commissioner is hereby authorized to charge any required fee for this Brief, or occasioned by this paper, or credit any overpayment in such a fee, to Deposit Account No. 50-0320.

RELIEF REQUESTED

It is respectfully requested that the rejection of claims 1-4, 6-10, 12 and 13 be reconsidered and withdrawn, and that a Notice of Allowance promptly issue.

STATUS OF THE CLAIMS

Claims 1-4, 6-10, 12 and 13 as set forth in Appendix A to the Appeal Brief, are rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over claim 2 of U.S. Patent No. 5,688,512 ("the 512 patent") in view of Cohen, Immunization, in Basic & Clinical Immunology, 3rd ed. Fudenberg HH, Stites DP, Caldwell JL, Wells JV, ed. 1980 (Cohen).[1]

ARGUMENT

THE REJECTION OF ALL CLAIMS UNDER THE JUDICIALLY CREATED DOCTRINE OF OBVIOUSNESS-TYPE DOUBLE PATENTING CANNOT STAND AND IS OVERCOME

I. *The Examiner's reliance on Cohen is fatally flawed and fails to supply the deficiences of 512 patent claim 2*

1. The Examiner provides no citations for his characterizations of and extrapolations from Cohen and thus the rejection is fatally flawed and must be vacated

At page 4 of the Examiner's Answer, the Examiner states:

> Cohen is a chapter from a textbook, utilized by the medical teaching profession, to discuss various vaccines and various routes of administration with mucosal administration.
>
> Thus, since the field of immunization as evidenced by the Cohen reference recognized mucosal administration of vaccines as but one of several appropriate routes of administration, it would have been obvious to one of ordinary skill in the art at the time the invention was made that mucosal/oral administration of the claimed composition was an obvious variant of the many routes of administration available.

At page 5 of the Examiner's Answer, the Examiner states: "Cohen teaches various administration routes for effective immune response induction depending upon the organism being used, including mucosal/oral administration. Thus, one of skill in the art would have been motivated to modify the subject matter of claim 2 ... to utilize one of the effective routes taught by Cohen, either mucosal or oral."

---

[1] The rejection of claims 1-4, 6-10, 12, and 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of the 512 patent in view of the related patent of Bergstrom et al., U.S. Patent No. 5,523,089 was withdrawn in the Examiner's Answer, at page 3, for which the Examiner is thanked.

The Examiner has not referred to specific portions of Cohen. He has left both Applicants and Board to speculate as to what portions of Cohen he relies upon and why Cohen would contain a teaching, suggestion, reason, motivation or incentive leading to the claimed invention. Thus, the rejection must *prima facie* fail. *See Ex parte Gambogi*, 62 USPQ2d 1209 (BOPAI 2001) (citing *In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981) and *In re Rijckaert*, 9 F.3d 1531, 1533, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) for the proposition that when the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the prior art, and recommending that the examiner use the practice set out in *Ex parte Braeken*, 54 USPQ2d 1110, 1112-1113 (BOPAI 1999), i.e., reproducing the claim with reference therein to column and line of relevant prior art reference, and vacating and remanding rejection because the examiner did not refer to specific portions of each of the cited references which left the Board and the Applicants to speculate as to portions of the reference relied upon) (copy attached as Exhibit A).[2]

2. The Examiner's characterizations of and extrapolations from Cohen are baseless and therefore the rejection must fail

Attached as Exhibit B, for the Board's convenient reference, is a copy of Cohen.[3]

The subject matter of the instant invention is active immunization by administering mucosally, preferably orally, OspA. OspA is an antigen of *Borrelia burgdorferi*; a subunit of *Borrelia burgdorferi*(*see* present application at page 3). OspA is not live *Borrelia burgdorferi* (*see id.*). Moreover, as discussed at page 2 of the instant application, Lyme disease, if allowed to progress, gives rise to cardiac, neurological and joint abnormalities. Further still, it is respectfully requested that judicial notice be taken of the fact that commercially available Lyme

[2] The Decision of Exhibit A was not presented sooner because it is a recent Board Decision that is supplied in direct response to the Examiner's Answer, and for the convenience of the Board. Thus, there is good and sufficient cause for Exhibit A presented herewith, as requested by 37 C.F.R. 1.195.

[3] In case Applicants and the Examiner are working from a different document with respect to that which has been cited as Cohen. Accordingly, as to the Examiner's citation of Cohen, Applicants are working from Exhibit B; and, the Board is invited to advise Applicants if they are working from a different document than that from which the Examiner is working in making the rejection. Comments herein as to Cohen are based on Exhibit B hereto, as that is what Applicants understand to be the Cohen document employed in the double patenting rejection. And of course, it is respectfully submitted that this confusion arises from the Examiner's failure to cite to specific portions of Cohen for his characterizations of and extrapolations from Cohen in Office Actions and the Advisory Action. Since Exhibit B is supplied for the convenience of the Board and due to the Examiner's failure to cite to specific portions of Cohen, particularly in the Examiner's Answer, such that Exhibit B is supplied in direct response to the Examiner's Answer, Applicants have provided good and sufficient cause for Exhibit B presented herewith, as requested by 37 C.F.R. 1.195.

Disease vaccines are and were administered by injection (*see* Exhibit C hereto, "FDA panel backs Lyme disease vaccine," CNN.com, May 26, 1998: "the first vaccine against Lyme disease ... LYMErix, requires three shots").[4]

More specifically, and as discussed in the Appeal Brief, the claims do not stand or fall together, and the claims are summarized as follows:

Claim 1 provides a mucosal administration of OspA. Claim 2 involves the mucosal administration of lipidated OspA. Claim 3 and the claims dependent thereon (claims 4, 6), and claim 9, as well as claim 13, involve oral administration. Claim 3, more particularly, calls for oral administration of lipidated OspA. Claim 4 specifies oral administration of lipidated OspA in a liquid. Claim 6 requires oral administration of lipidated OspA without any immunogenicity-enhancing adjuvant. Claim 7 calls for mucosal administration of recombinant OspA. Claim 8 involves mucosal administration of recombinant lipidated OspA. Claim 9 provides for oral administration of recombinant lipidated OspA. Claim 10 is directed to mucosal administration of recombinant lipidated OspA obtained by: transforming a host organism by a plasmid containing a gene coding for a full-length wild-type *Borrelia burgdorferi* OspA lipoprotein and producing recombinant *Borrelia burgdorferi* OspA lipoprotein, and purifying the recombinant *Borrelia burgdorferi* OspA lipoprotein substantially free from other bacterial proteins, and from lipopolysaccharide, under non-denaturing conditions from a lysate of the host organism so as to obtain a purified recombinant *Borrelia burgdorferi* lipoprotein which remains lipidated and is in a form administrable to the host. And, claim 12 calls for mucosal administration of an OspA composition in the form of a solution, suspension, emulsion, syrup, elixir, capsule, tablet, hard-candy-like preparation, or a solid food item, i.e., oral administration.

The undersigned respectfully does not see in Cohen "various routes of administration with mucosal administration merely one route of several," as asserted in the Examiner's Answer; or, in fact, any bases in Cohen for the characterizations of and extrapolations from Cohen set forth in the Examiner's Answer.

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[4] Exhibit C is provided in direct response to the Examiner's Answer and could not have been presented sooner, and is provided for the convenience of the Board to take notice of a known fact that is also stated in the present application. Thus, Applicants have provided good and sufficient cause for presenting herewith Exhibit C, as requested by 37 C.F.R. 1.195. *See also* present application at page 25: "in human field trials, rOspA was administered subcutaneously (3)" and Erdile et al., Infect. Immun. 1993, 61, 81-90 cited in reference (3) of the present application and the foregoing quote.

Rather, various materials for active immunization are set out in Table 43-3 of Cohen. With the exception of the live poliovirus vaccine, all of the materials in Cohen's Table 43-3 are administered via injection, namely, subcutaneously ("subcut"), intramuscularly ("IM"), and intradermally ("intradermal"). The live poliovirus is given orally due to the nature of poliovirus (e.g., poliovirus is an enterovirus transmitted by the fecal-oral route); the inactivated poliovirus is administered by injection (note the entry at page Table 43-3, page 715 of Cohen for killed virus).

As the present invention does not involve a live virus, or an enterovirus, or poliovirus, or even a pathogen transmited by the fecal-oral route, the mere mention of "oral" in Cohen's Table 43-3 fails to show that "mucosal administration [is] but one of several appropriate routes of administration" as asserted in the Examiner's Answer.

The only other mention the undersigned can locate in Cohen of routes of administration is at page 712 and reads:

> The route of immunization may be an important determinant of successful vaccination, particularly if nonreplicating immunogens are employed. Thus, immunization intranasally or by aerosol often appears to be more successful than parenteral injection against viral or bacterial challenges to the respiratory tree.

If anything, this passage in Cohen teaches away from the instant invention. Lyme disease – or *Borrelia burgdorferi* infection – is the result of a tick bite; and is not a challenge to the respiratory tree. This passage cautions that the route of administration is important for successful vaccination, and directs the skilled artisan towards routes of administration that are commensurate with how the pathogen challenges the host. Accordingly, following this passage in Cohen, the skilled artisan is directed towards administering a Lyme Disease vaccine by way of an injection (since *Borrelia burgdorferi* infection is the result of a tick bite).

In sum, the characterizations of and extrapolations from Cohen set forth in the Examiner's Answer simply cannot be found in Cohen. If anything, Cohen teaches away from the instant invention, by directing towards administration via injection. Accordingly, the rejection must fail.

II. *The Examiner fails to show why one would be motivated to modify 512 patent claim 2 for oral or mucosal administration or for any of the other recitations of the claims, which do not stand or fall together*

1. The Examiner fails to make a *prima facie* case of obviousness

The Examiner's Answer admits that the claims do not stand or fall together and asserts that the present claims are obvious over claim 2 of the 512 patent in view of Cohen.

However, other than the above-described fatally-flawed reliance upon Cohen (which actually teaches away from the present invention and towards administration via injection), the Examiner's Answer only cites to column 18, lines 30-38 of the 512 patent, and fails to address each of the recitations of claims 1, 2-4, 6-10, 12 and 13 of the instant application.

While Applicants disagree with reliance upon the specification of the 512 patent to support an obviousness-type double patenting rejection,[5] it is noted that the cited portion of the 512 patent mentions "**any immunization route**" including "oral ... subcutaneous, intracutaneous or intramuscular ... nasal or rectal" (emphasis added).

As discussed in the Appeal Brief, an analysis in a double patenting rejection parallels the analysis of a Section 103 rejection. Under Section 103, it is well established that "there must be some reason for the combination other than the hindsight gleaned from the invention itself". *Uniroyal v. Rudkin-Wiley*, 5 USPQ 2d 1434, 1438 (Fed. Cir. 1980). There also must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the primary reference in the manner suggested by the Examiner. *In re Laskowski*, 12 USPQ 2d 1397, 1399 (Fed. Cir. 1989). Also, "obvious to try" is not the standard under 35 USC §103. *In re Fine*, 5 USPQ 2d 1596, 1599 (Fed. Cir. 1988). Further, as stated by the Court in *In re Fritch*, 23 UPPQ 2d 1788, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification."

Thus, it is respectfully submitted that the burden was on the Examiner, in the Examiner's Answer, to provide teachings, suggestions, incentive or motivation to modify 512 patent claim 2 to arrive at each of claims 1, 2-4, 6-10, 12 and 13 of the instant application. The Examiner has failed to meet his burden.

Indeed, the Examiner's Answer fails to provide any teaching, suggestion, incentive, or motivation in the art to modify the scope of 512 patent claim 2, namely "**any immunization route**" to mucosal immunization, or more particularly, to oral immunization.

More generally, the Examiner's answer fails to contain a particular analysis of each of claims 1, 2-4, 6-10, 12 and 13 of the instant application; and thus, the Examiner's Answer fails to

[5] According to *In re Kaplan*, 229 USPQ 678, 683 (Fed. Cir. 1986), I*n re Braithwaite*, 154 USPQ 29 (CCPA 1967) and MPEP 804 (*see* Eighth Edition, August 2001 at page 800-22), the disclosure of the 512 patent may not be used by the Examiner in making the present double patenting rejection because only the claims of 512 patent, not its disclosure, are available for use in a double patenting rejection; *see also* discussion *infra*.

provide specific teachings, suggestions, incentives or motivations in the art to modify 512 patent claim 2 to arrive at each of the recitations of claims 1, 2-4, 6-10, 12 and 13. Simply, the Examiner's Answer fails to provide the suggestion of each of claims 1, 2-4, 6-10, 12 and 13 from 512 patent claim 2.

Indeed, administration of antigens by injection, e.g., subcutaneously, generally elicits the strongest responses probably because the antigen is taken up by Langerhans' cells and efficiently presented in lymph nodes; specific antibodies or T cells against a given antigen are elicited when administration is by injection.[6] Thus, the art generally directs the skilled artisan towards administration of an antigen by injection.[7] Note again how, as discussed above, Cohen provides mainly for administration by injection and directs towards administration by injection, with the undersigned finding only one reference in Cohen to oral administration, i.e., as to poliovirus, and only one reference in Cohen as to aerosol administration, i.e., with respect to challenges of the respiratory tree.[8]

Administration mucosally or orally typically elicits a local response; and moreover, antigens administered orally may be destroyed by the gastrointestinal tract prior to eliciting any response.[9] Hence, mucosal administration, and particularly oral administration, is not generally favored.

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[6] *See* Janeway et al., Immunobiology pp616-617 (5th Ed. 2001) (copy attached as Exhibit D). Exhibit D is supplied herewith in direct response to the Examiner's Answer. More specifically, the Examiner's Answer, it is respectfully submitted, mischaracterizes Cohen, incorrectly extrapolates from Cohen, and incorrectly makes statements about the art to which the present application pertains, e.g., by attempting to equate all routes of administration and by attempting to assert that recitations of the claims are obvious. Janeway et al. is not prior art as to the instant application, and is supplied in direct rebuttal to the Examiner's Answer to show that even today the state of the art is not as asserted in the Examiner's Answer. As Janeway et al. is in direct rebuttal to the Examiner's Answer, it could not have been presented sooner. Accordingly, Applicants have provided good and sufficient cause for prsenting herewith Exhibit D as requested by 37 C.F.R. 1.195.

[7] *See* Janeway et al., *supra* (Exhibit D), note, for instance: "Antigen administration via the gastrointestinal tract is used mostly in the study of allergy. ... Introduction of antigen into the respiratory tract is also used mainly in the study of allergy."

[8] There is nothing in the art that equates poliovirus and *Borrelia burgdorferi* or that equates *Borrelia burgdorferi* with pathogens that challenge the respiratory tree, or that allows extrapolation from poliovirus to *Borrelia burgdorferi*, or that allows extrapolation from pathogens that challenge the respiratory tree to *Borrelia burgdorferi*. Hence, there is nothing in Cohen that teaches, suggests, motivates, directs, provides incentive, or allows modification of the general teachings of 512 patent claim 2 to arrive at the instant invention; and therefore, the double patenting rejection, it is respectfully submitted, must fail.

[9] *See* Janeway et al., *supra* (Exhibit D). *See also* Examples of present application: orally administered OspD did not result in the production of OspD-specific antibodies, which led the to the investigation of the relative trypsin sensitivities of rOspA and rOspD (present application pages 22-23); rOspD was digested into peptide fragments by 0.03125 µg/ml trypsin – a four-fold difference in sensitivity to trypsin (when compared with rOspA sensitivity to trypsin). "Sensitivities of rOspA and rOspD to trypsin and low pH were investigated in an attempt to explain the difference in immunogenicity of these lipoproteins when administered orally. It was thought that the gastric acidity

Thus, there is no incentive, direction or motivation in the art to modify the general teachings of 512 patent claim 2 to arrive at the instant invention.

More in particular, there is no incentive, direction or motivation in the art to modify the teachings of 512 patent claim 2 to administer OspA mucosally, and particularly orally. Again, it is noted that oral administration is a component of claims 3, 4, 6, 9, 12 and 13.[10]

Furthermore, OspA is a protein.[11] It is also well known in the art that most proteins are poorly immunogenic or nonimmunogenic.[12] Accordingly, most vaccines contain an adjuvant – an immunogenicity-enhancing ingredient[13]. There was no incentive, direction or motivation in the art to modify 512 patent claim 2 to orally administering OspA without any immunogenicity-enhancing adjuvant, as called for in claim 6.[14]

Moreover, the Examiner's Answer fails to provide any teachings, suggestions, incentive or motivation to modify the 512 patent claim 2 teachings to arrive at the mucosal administration of lipidated OspA as called for in claims 2 and 8 of the instant application.[15]

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or trypsin in the small intestine may affect these proteins differenty and thereby influence the antibody response to them. ... The molecular structure of rOspA lipoprotein may facilitate its absorption into the gastrointestinal tract ... It appears that gastric acidity does not affect the ability of OspA to be taken up and transported by cells in the gastrointestinal tract ... It is not known whether rOspD is stable in acidic conditions. Such differences in biochemical properties of these proteins may explain the apparent failure of rOspD to elicit a detectable antibody response when administered via the oral route" (present application pp 26, 27-28).

[10] *See also* Examples of present application (especially present application at pages 25, 28): Orally administered OspA provided 100% protection against infection by *B. burgdorferi* – a surprisingly superior result, not taught or suggested by 512 patent claim 2, alone or in combination with Cohen, that evinces the patentability of the present invention. *See In re Chupp*, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987) ("[t]o be patentable, a compound need not excel over prior art compounds in all common properties. . . . Evidence that a compound is unexpectedly superior in one spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness").

[11] "OspA" stands for "Outer surface protein A".

[12] *See* Janeway et al., *supra* (Exhibit D) ("Most proteins are poorly immunogenic or nonimmunogenic when administered by themselves. Strong adaptive immune responses to protein antigens almost always require that the antigens be injected in a mixture known as an adjuvant. An adjuvant is any substance that enhances the immunogenicity of substances mixed with it.").

[13] *See* Janeway et al., *supra.*

[14] *See also* Examples of present application (especially pages 25, 28): Orally administered OspA "without adjuvant or additional ingredients which could enhance immunogenicity" provided 100% protection against infection by *B. burgdorferi* – a surprisingly superior result, not taught or suggested by 512 patent claim 2, alone or in combination with Cohen, that evinces the patentability of the present invention. *See In re Chupp*, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987) ("[t]o be patentable, a compound need not excel over prior art compounds in all common properties. . . . Evidence that a compound is unexpectedly superior in one spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness").

[15] *See also* Examples of present application (and especially page 29): "since the herein protective results are from isolated, purified recombinant lipidated OspA without adjuvant, it is believed ... that the lipidation of the OspA may be providing the protective results." *See In re Chupp*, 2 U.S.P.Q.2d 1437, 1439 (Fed. Cir. 1987) ("[t]o be patentable, a compound need not excel over prior art compounds in all common properties. . . . Evidence that a compound is unexpectedly superior in one spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness"). Note further that claim 8 calls for OspA (of claim 7 – rOspA) to be lipidated; and, that claim 9,

And, the Examiner's Answer fails to provide any teachings, suggestions, incentive or motivation to modify the 512 patent claim 2 teachings to arrive at the mucosal administration of recombinant OspA ("rOspA"), as called for by claim 7, or to arrive at the mucosal administration of lipidated rOspA as called for by claim 8, or most particularly, a lipidated rOspA obtained by the particular method steps recited in claim 10.

Clearly, the Examiner has failed to make out a *prima facie* case of obviousness of the present claims in view of claim 2 of the 512 patent, either individually, or in combination with Cohen. Therefore, the double patenting rejection must fail.

Accordingly, reconsideration and withdrawal of the rejection of claims 1 to 4, 6 to 10, 12 and 13 under the judicially created doctrine of obviousness-type double patenting is warranted and such relief is respectfully requested.

III. *The Examiner's reliance on text of the 512 patent is tantamount to a new rejection in the Examiner's Answer such that the rejection must be vacated, and that reliance on the text of the 512 patent is improper and based on a misunderstanding of the 512 patent claims and their prosecution*

1. The Examiner's new reliance on the text of the 512 patent in the Examiner's Answer is tantamount to a new rejection in the Examiner's Answer, and thus the rejection must be vacated

As noted above, the rejection of claims 1-4, 6-10, 12, and 13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of the 512 patent in view of the related patent of Bergstrom et al., U.S. Patent No. 5,523,089 was withdrawn in the Examiner's Answer, at page 3. However, it is respectfully submitted that only now, in the Examiner's Answer, for the very first time in the prosecution, is the Examiner relying upon the text of the 512 patent, i.e., only now in the Examiner's Answer, after Applicants correctly pointed out in the Appeal Brief that the Examiner could not rely upon the text of the 512 patent via the 089 patent is the Examiner relying upon the text of the 512 patent. In other words, the Examiner's Answer is the very first time in this prosecution that the Examiner is relying upon the text of the 512 patent.

37 C.F.R. 1.193(a)(2) prohibits an Examiner's Answer from containing a new ground of rejection.

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dependent upon claim 8, calls for oral administration, such that claim 9 calls for oral administration of lipidated rOspA, which has been shown in the present application to afford 100% protection against *Borrelia burgdorferi*, a

It is respectfully submitted that the newfound reliance upon the text of the 512 patent is tantamount to a new ground of rejection in the Examiner's Answer.

Thus, the rejection of claims 1 to 4, 6 to 10, 12 and 13 under the judicially created doctrine of obviousness-type double patenting in the Examiner's Answer, it is respectfully submitted, should be vacated because it is a new ground of rejection in the Examiner's Answer. It is respectfully requested that the Honorable Board vacate the double patenting rejection in the Examiner's Answer.

2. The Examiner's reliance on the text of the 512 is improper and based on a misunderstanding of the 512 patent claims and their prosecution; thus, the rejection should be reversed

According to *In re Kaplan*, 229 USPQ 678, 683 (Fed. Cir. 1986), I*n re Braithwaite*, 154 USPQ 29 (CCPA 1967) and MPEP 804 (*see* Eighth Edition, August 2001 at page 800-22), the disclosure of the 512 patent may not be used by the Examiner in making the present double patenting rejection because only the claims of 512 patent, not its disclosure, are available for use in a double patenting rejection.

The Examiner's Answer cites to MPEP 804 to attempt to justify improperly relying upon the text of the 512 patent in making the double patenting rejection; that is, the Examiner's Answer cites to MPEP 804 for the proposition that specification can always be used as a dictionary to learn the meaning of a term in the patent claim, and, that those portions of the specification which provide support for the patent claims may also be examined and considered in making a double patenting rejection.

The Examiner's Answer is flawed because the text of the 512 patent need not be consulted to define any term of claim 2 of the 512 patent; the terms of 512 patent claim 2 are used in accordance with the ordinary meaning ascribed to them by the skilled artisan. Thus, the "dictionary" justification of MPEP 804 for turning to the specification text does not apply in the instant situation.

Further still, the Examiner's Answer is flawed because when 512 patent claim 2 is properly construed, neither the "provide support" nor the "dictionary" justifications of MPEP 804 for turning to the specification text apply in the present situation.

More specifically, MPEP 804 calls upon the Examiner to make *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), factual inquiries that are summarized as follows: (A)

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surprising and unexpected result. *See In re Chupp.*

determine the scope and content of a patent claim and the prior art relative to a claim in the application at issue; (B) determine the differences between the scope and content of the patent claim and the prior art as determined in (A) and the claim in the application at issue; (C) determine the level of ordinary skill in the pertinent art; and (D) evaluate any objective indicia of nonobviousness.

These inquiries, and particularly determinations (A) and (B) requires a claim construction of the patent claim; and thus, so too does any attempt to rely upon the "provide support" or "dictionary" justifications of MPEP 804 for turning to the specification text.[16] Claim construction involves consideration of (1) the language of the patent claim itself, (2) the specification, (3) other claims and (3) the prosecution history. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996).

The Board and the Examiner are respectfully invited and requested to review the prosecution history of the 512 patent – which, it is respectfully submitted, is available to the Board and the Examiner. As is evident from the prosecution history of the 512 patent, during the prosecution of the 512 patent, there was a demonstration of administering OspA via injection (subcutaneously) to dogs by way of a Declaration of Dr. Judy Jarecki-Black.[17] Simply, when 512 patent claim 2 is construed in the light of the prosecution history of the 512 patent, it is respectfully submitted that the Examiner's reliance in the Examiner's Answer on the text of the 512 patent is misplaced and not justified by MPEP 804.

Thus, the reliance in the Examiner's Answer on the text of the 512 patent is improper; and, for this reason too, it is respectfully requested that the double patenting rejection be reconsidered and withdrawn.

Furthermore, as discussed in the Appeal Brief, Examiner Hazel Sidberry was the original Examiner on the present application. Examiner Hazel Sidberry indicated that the claims of the present application were allowable (without any double patenting rejection based on the 512

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[16] Simply, one cannot assert that which is required to "support" a patent claim or define a patent claim term, without a claim construction analysis: A patent claim is not a patent application claim and is therefore not subject to MPEP 2111. Accordingly, the Examiner must perform a claim construction analysis consistent with how the case law calls for patent claims to be construed, before there can be resort to the specification of a patent in making a double patenting rejection.

[17] A copy of that Declaration is attached as Exhibit E, for the convenient reference of the Board and the Examiner, such that Exhibit E is supplied in direct rebuttal to the Examiner's Answer (e.g., as the Examiner's Answer, for the first time in the prosecution of the present application cites to the 512 patent text); and thus, Applicants have also shown good and sufficient cause for why Exhibit E is herewith presented, as requested in 37 C.F.R. 1.195.

patent; *see* Examiner Summary of February 10, 1998 Interview in the present application). Examiner Hazel Sidberry was also the Examiner on the 512 patent. Examiner Hazel Sidberry was armed with personal knowledge of the prosecution of the 512 patent. She did not make a double patenting rejection in the instant application based on claim 2 of the 512 patent. Deference should be paid to her experience, including her personal knowledge of the prosecution of the 512 patent, and her original determination as to the allowability of the claims of the instant application; and, such deference is respectfully requested, especially in view of the foregoing and the arguments in the Brief on Appeal. And on this point, it is noted that the Examiner's Answer provides no basis for why there should not be deference to Examiner Sidberry's previous determination in the present application of allowability. Therefore, deference should be paid to Examiner Sidberry's previous determination of patentability of the instant claims; and, for this reason too, the double patenting rejection should be reconsidered and withdrawn, with such relief respectfully requested.

IV. *The Examiner has failed to properly consider the indicia of nonobviousness provided in the instant application*

1. The MPEP requires consideration of indicia of nonobviousness; throughout this text and the present application there is evidence of nonobviousness that the Examiner has failed to consider; hence, the double patenting rejection should be reconsidered and withdrawn

As discussed above, MPEP 804 mandates, *inter alia*, that the Examiner evaluate any objective indicia of nonobviousness. As also discussed in this paper, e.g., in various footnotes and main text throughout this paper, the present application contains evidence of surprising and unexpected results achieved by the instant invention. It is respectfully submitted that the Examiner has failed to consider the surprising and unexpected results achieved by the instant invention, as demonstrated in the present application, and as discussed in this paper, e.g., the various footnotes and main text throughout this paper. Accordingly, it is respectfully asserted that the Examiner has failed to properly follow the mandates of MPEP 804 in making the double patenting rejection.

Moreover, in view of the surprising and unexpected results achieved by the instant invention, as demonstrated in the present application, and as discussed in the various footnotes and main text throughout this paper, the double patenting rejection is clearly erroneous and should be reconsidered and withdrawn.

In this regard too, it is again noted that the claims do not stand or fall together. And it is particularly further noted that the surprising and unexpected results of the instant invention are above argued with respect to "oral administration" claims 3, 4, 6, 9, 12 and 13; "oral administration without immunogenicity-enhancing adjuvant" claim 6; "mucosal administration of lipidated OspA" and "mucosal administration of lipidated rOspA" claims 2 and 8; and "oral administration of lipidated rOspA" claim 9, *inter alia* (*see, e.g.,* footnotes 9, 10, 14, 15, *supra*, and main text accompanying these footnotes, *inter alia*). So as to not be repetitive, it is mentioned that the foregoing arguments and footnotes that assert the surprising and unexpected results of the instant invention, especially as to particular claims, are hereby incorporated herein, at this point, by reference, with the Board and the Examiner respectfully invited and requested to review the foregoing.

Thus, it is respectfully requested that the double patenting rejection be reconsidered and withdrawn in view of the surprising and unexpected results achieved by the instant invention, as demonstrated in the present application, and as discussed in the various footnotes and main text throughout this paper.

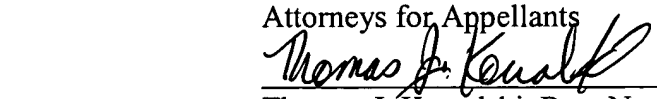
CONCLUSION

For the reasons discussed in this Brief, the Appeal Brief, and the arguments of record (incorporated herein by reference), claims 1-4, 6-10, 12 and 13 are patentable over claim 2 of the 512 patent, either individually or in combination with Cohen. It is, therefore, respectfully submitted that the Examiner erred in rejecting claims 1-4, 6-10, 12 and 13, and a reversal of the rejection of claims 1-4, 6-10, 12 and 13 by this Honorable Board, and prompt issuance of a Notice of Allowance, are earnestly solicited.

Respectfully submitted,

FROMMER LAWRENCE & HAUG, LLP

Attorneys for Appellants



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FULL TEXT OF CASES (USPQ2D)
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(Unpublished) Ex parte Gambogi, 62 USPQ2d 1209 (BdPatApp&Int 2001)

62 USPQ2D 1209
Ex parte Gambogi
U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences

Appeal No. 2001-1022
Decided December 10, 2001

Unpublished Opinion

(Non-precedential)

Headnotes

PATENTS

[1] Practice and procedure in Patent and Trademark Office — Board of Patent Appeals and Interferences — Rules

and rules practice (§110.1105)

Patentability/Validity — Obviousness — Relevant prior art — In general (§115.0903.01)

Rejection of claims in patent application under 35 U.S.C. §103(a) must be vacated and remanded, since patent examiner has cited numerous

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references in support of rejection, but has not indicated what that prior art would have meant to person of ordinary skill in art, since examiner has not referred to specific portions of each of cited references, and since rejection therefore requires both applicants and Board of Patent Appeals and Interferences to speculate as to portions of each reference relied upon, and why those references would contain teaching, suggestion, motivation, or incentive leading to claimed invention; in entering any new rejection, examiner should adopt practice described in Manual of Patent Examining Procedure for setting forth Section 103(a) rejection in office action, and should reproduce rejected claim or claims with reference therein to column and line of each relevant prior art reference.

Case History and Disposition

Patent application of Robert J. Gambogi, Steven W. Fisher, Edward A. Tavss, and Marilou T. Joziak, serial no. 09/065,267.1 Applicants appeal from examiner's final rejection of claims 1-15 in application. Vacated and remanded.

[Editor's Note: The Board of Patent Appeals and Interferences has indicated that this opinion is not binding precedent of the board.]

Judge:

Before Winters and William F. Smith, administrative patent judges, and McKelvey, senior administrative patent judge.

Footnotes

1 Application for patent filed 23 April 1998. The real party in interest is Colgate-Palmolive Co. (Appeal Brief, page 2).

Opinion Text

Opinion By:

McKelvey, S.J.

Decision on appeal under 35 U.S.C. §134

The appeal is from a decision of a primary examiner rejecting claims 1-15. We *vacate* and *remand* for further proceedings not inconsistent with the views expressed in this opinion.

A. Findings of fact

The record supports the following findings by at least a preponderance of the evidence.2

The invention

1. The claimed invention relates to (1) a two-component dental composition and (2) a method of using the composition.

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The examiner's rejections

2. According to the Examiner's Answer (Paper 11,3 page 4), the rejection is set out in the Final Rejection (Paper 4).

3. The final rejection makes the following rejections (page 3):

Claims 1-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Campbell et al. (I-II-III) or Fisher et al. U.S. 5,780,015 (details noted above) taken with any one of each of: Toy, newly cited, Fischer, Collins et al., or Norfleet et al. (I-VI) * * *.

4. The rejection, stated in different terms, is as follows:

Claims 1-15 are rejected under 35 U.S.C. §103(a) as being unpatentable over the following prior art references, each of which is a U.S. patent:

(1) Campbell I,
(2) Campbell II,
(3) Campbell III *or*
(4) Fisher 4

taken with any one of:

(a) Toy,
(b) Fischer,
(c) Collins,
(d) Norfleet I,
(e) Norfleet II,
(f) Norfleet III,

(g) Norfleet IV,
(h) Norfleet V *or*
(i) Norfleet VI.

5. A person with rudimentary skills in mathematics will immediately appreciate the fact that the examiner has entered no less than 36 separate rejections (i.e., 4 times 9 equals 36).

6. According to the final rejection (page 4), each of the Norfleet patents is said to describe a hydroxide with a pH of 6 to 8, preferably 7. No reference is made to a column and/or line of any of the Norfleet patents.

7. Further according to the final rejection (page 4), Collins is said to describe the hydroxide and a pH of 6 to 8. No reference is made to a column and/or line of Collins.

8. Still further according to the final rejection (page 4), "especially"Fischer describes two other hydroxides and a pH of 4 to 9, preferably 5 to 7. No reference is made to a column and/or line of Fischer.

9. Certain compositions are said to be described by each of the three Campbell patents and Fisher.

10. There follows a reference to page 4, lines 1-7 of some document. The reference may be to page 4, lines 1-6 of applicants' specification.

11. Claim 1 contains limitations reading a "component containing"two ingredients and a "component containing" one ingredient.

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12. The examiner asserts, without any underlying analysis, that "containing"is "open-ended", i.e., means "comprising." Ultimately, the examiner suggests that "containing" should be replaced with "consisting essentially of".

13. The examiner's final rejection is basically uninformative, if not unintelligible.

The appeal brief

14. Notwithstanding the vague nature of the final rejection, applicants make a reasonable attempt in the Appeal Brief (Paper 10) to explain why the final rejection is wrong.

15. Not without reason, applicants interpret the examiner's suggestion to replace "containing" with "consisting essentially of"as some form of rejection under 35 U.S.C. §112, second paragraph. Ultimately, in the Examiner's Answer (Paper 11, page 9), the examiner attempts to make clear that no §112 rejection was made.

16. With commendable patience, applicants attempt to address the examiner's rejections—rejections which basically cannot be addressed because they are so vague.

Examiner's answer

17. The Examiner's Answer (Paper 11) does little to clarify the examiner's otherwise vague rejections.

18. At one point in the Examiner's Answer (Paper 11, page 3), the examiner asserts that "the appealed claims clearly encompasses prior art * * * patents * * *" leaving the possible impression that one or more claims are unpatentable under 35 U.S.C. §102 for anticipation.

19. The examiner says that claims 1-15 stand or fall together (Paper 11, page 3) when applicants make perfectly clear that claims 1-7 are one group (compositions claims) and claims 8-15 are another group (process claims).

20. In the Examiner's Answer, and for the first time in the prosecution, the examiner takes what we believe the examiner thought was official notice of a fact that certain salts are not stable in certain environments (page 4), citing §2144.03 of the *Manual of Patent Examining Procedure.*

21. The examiner goes on to state, without citation to the page and line of any document, that applicants admit certain facts.

22. According to the examiner, one of the prior art references "admittedly discloses" certain facts, although absolutely no reference is made to a column and/or line of the reference or where the applicants are said to have made any admission.

23. Nothing in the Examiner's Answer clarifies in any material way the vague rejections made in the final rejection.

24. Interestingly enough, applicants filed no reply brief, and with good reason. We find no fault with applicants having declined to file a reply brief. We would have found it difficult, given the prosecution, to respond to the Examiner's Answer.

B. Discussion

1.

The board in an ex parte appeal is basically a board of review—we review final rejections made by patent examiners. In order to have

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meaningful review, we must be able to understand the examiner's rejection, or in this case the examiner's 36 rejections. This appeal reminds us of *In re Herrick*, 344 F.2d 713, 145 USPQ 400 (CCPA 1965). There the CCPA said (*id.* at 716, 145 USPQ at 400):

> We have begun our consideration of the rejections in this case with a purely numerical analysis, and we have ended it there, for, as will become apparent, the existing situation does not permit rational isolation and determination of the legal issues which may be present.

The CCPA went on to state (*id.* at 716, 145 USPQ at 401):

> The form of the rejection would seem to indicate that many of the references were considered merely cumulative. And yet, the examiner's answer * * * describe[s] and analyze[s] each reference in some detail.[5] Such a state of affairs places this court in a very real quandary. Are we to choose one individual rejection for each claim and turn the entire appeal on the correctness of those rejections? Or are we to work our way step-by-step through each rejection in the hope of finding one we can sustain? Neither alternative is satisfactory from the standpoint of the public interest.
>
> * * *
>
> We decline to substitute speculation as to the rejection for the greater certainty which should come from the Patent Office in a more definite statement of the grounds of rejections. To the extent that the references are *truly* cumulative, the examiner or board can so indicate. If, on the other hand, all or most of the references are really necessary to meet the claims, the rejection can be made specific as to particular references.

What the CCPA said in *Herrick* applies to this case.

[1] There may be times when the use of numerous references can be justified. *Cf. In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991) (the criterion is not the number of references, but what they would have meant to a person of ordinary skill in the art). In this case, however, the examiner has not told applicants or the board what the prior art would have meant to a person skilled in the art. Moreover, the examiner has not referred to specific portions of each of the references. *Cf. In re Yates*, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151(CCPA 1981), which the Federal Circuit in *In re Rijckaert*, 9 F.3d 1531, 1533, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993), characterized as holding that when the PTO asserts that there is an explicit or implicit teaching or suggestion in the prior art, it must indicate where such a teaching or suggestion appears in the prior art). Thus, both applicants and the board have to speculate as to the portions of each reference relied upon and why those references would contain a teaching, suggestion, reason, motivation or incentive leading to the claimed invention.

We decline to tell an examiner precisely how to set out a rejection. We recommend that in entering any new rejection in the application on appeal that the examiner adopt the practice set out in §706.02(j) of the *Manual of Patent Examining Procedure* which contains a discussion of what an examiner should set forth in an Office action when making a rejection under 35 U.S.C. §103(a). Moreover, we additionally recommend that the examiner use the practice set out in *Ex parte Braeken*, 54 USPQ2d 1110, 1112-1113(Bd. Pat. App. & Int. 1999), i.e., reproducing the claim with reference therein to the column and line of a relevant prior art reference.

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2.

There are numerous other difficulties with the appeal.

a.

We find it somewhat curious that the examiner found it necessary to cite and rely on Toy in the final rejection, while at the same time continuing to rely on numerous other possibly cumulative references. On the one hand, Toy is said to be necessary in view of amendments made by applicants (Paper 4, page 4). On the other hand, the examiner continues to alternatively rely on Fischer, Collins or any one of the six Norfleet patents. If Toy contains disclosure not contained by Fischer, Collins or the six Norfleet patents and Toy is necessary to meet the claims as amended, then why would it be necessary to continue to rely on Fischer, Collins and the six Norfleet patents.

b.

We also find that the examiner appears to have taken official notice of certain facts in the first instance in the Examiner's Answer. Taking official notice of facts for the first time in an Examiner's Answer would not appear to be consistent with the complete examination required by 37 CFR §1.104. If the facts officially noticed are necessary, the time for taking official notice is in the first action when an applicant has a meaningful opportunity to challenge the correctness of the fact officially noted.

c.

The examiner has alleged that applicants have admitted certain facts. When an examiner alleges that an applicant has admitted certain facts, the examiner is manifestly under a burden of citing the precise page and line of the document in which the admission occurred. Otherwise, the applicant will have difficulty addressing any issue of whether an admission has been made.

We recognize that in this case the examiner could say that applicants had an opportunity in a reply brief to challenge the correctness of the fact officially noted and the facts said to have been admitted. While it is true that applicants did not file a reply brief in this appeal, it is also true that the examiner's rejection is so vague that filing of a reply brief might well have been considered a futile act on the part of the applicants. Nothing in the Examiner's Answer materially clarified the vague final rejection. Hence, the absence of a reply brief is no basis upon which to penalize applicants in this particular case. It is not an applicant's responsibility to set out a clear and concise rejection in their reply brief—setting out a rejection is the responsibility of the examiner.

d.

In the final rejection, the examiner held that "containing" is an open-ended "transitional"phrase having the same meaning as "comprising" (Paper 4, page 3). The issue of whether "containing" is open-ended, like "comprising,"or means something else, like "consisting essentially of" or "consisting", is a matter which should be evaluated on a case-by-case basis. *Cf.* the discussion under OTHER TRANSITIONAL PHRASES in § 2111.03 of the *Manual of Patent Examining Procedure* (discussing prior court interpretations of "having" and "composed of"). *See also Crystal Semiconductor Corp. v. Tritech Microelectronics International, Inc.*, 246 F.3d 1336, 1348 (Fed. Cir.

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2001) ("having" does not create a presumption that the body of the claim is open; rather the claim must be examined in its full context to determine whether "having"limits the claims to its recited elements); *AFG Industries, Inc. v. Cardinal IG Co., Inc.*, 239 F.3d 1239, 1245, 57 USPQ2d 1776, 1780(Fed. Cir. 2001) ("composed of" in this case was interpreted to be the same as "consisting essentially of").

C. Order

Upon consideration of the appeal, and for the reasons given, it is

ORDERED that the examiner's rejection of claims 1-15 over the prior art as set out in the final rejection is *vacated*.6

FURTHER ORDERED that the application is *remanded* to the examiner for action not inconsistent with the views expressed in this opinion.

FURTHER ORDERED that nothing in this opinion should be read as precluding the examiner from entering a new rejection.

FURTHER ORDERED that we express no views on the ultimate merits of any rejection under 35 U.S.C. §103(a) based on the prior art references or any additional prior art which the examiner and applicant may wish to make of record.

FURTHER ORDERED that no time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR §1.136(a).

VACATED and REMANDED

Footnotes

2 To the extent these findings of fact discuss legal issues, they may be treated as conclusions of law.

3 The "contents"of the file wrapper of the application on appeal identify the Examiner's Answer as Paper 11. The Examiner's Answer, on the other hand, bears "Paper No. 10". According to the "contents," the Appeal Brief is Paper 10.

4 The reader should be aware that the examiner has relied on a "Fischer"and a "Fisher" reference which are different references.

5 In the appeal before us, apparently unlike the appeal in *Herrick*, the examiner has *not* analyzed each reference in any meaningful detail.

6 The effect of a decision vacating an examiner's rejection is explained in *In re Zambrano*, 58 USPQ2d 1312 (Bd. Pat. App. & Int. 2001) (noting that vacated rejection no longer exists).

- End of Case -

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43 | Immunization

Stephen N. Cohen, MD

IMMUNIZATION AGAINST INFECTIOUS DISEASES

It has been recognized for centuries that individuals who recover from certain diseases are protected from recurrences. The moderately successful but hazardous introduction of small quantities of fluid from the pustules of smallpox into the skin of uninfected persons (variolation) was an effort to imitate this natural phenomenon. Jenner's introduction of vaccination with cowpox (1796) to protect against smallpox was the first documented use of a live attenuated viral vaccine and the beginning of modern immunization. Koch demonstrated the specific bacterial cause of anthrax in 1876, and the etiologic agents of several common illnesses were rapidly identified thereafter. Attempts to develop immunizing agents followed (Table 43–1).

Table 43–1. Historical milestones in immunization.

Variolation	1721
Vaccination	1796
Rabies vaccine	1885
Diphtheria toxoid	1925
Tetanus toxoid	1925
Pertussis vaccine	1925
Viral culture in chick embryo	1931
Yellow fever vaccine	1937
Influenza vaccine	1943
Viral tissue culture	1949
Poliovaccine, inactivated (Salk)	1954
Poliovaccine, live, attenuated (Sabin)	1956
Measles vaccine	1960
Tetanus immune globulin (human)	1962
Rubella vaccine	1966
Mumps vaccine	1967
Hepatitis B vaccine	1975

Types of Immune Response

Immunization results in the production of antibodies directed against the infecting agent or its toxic products; it may also initiate cellular responses mediated by lymphocytes and macrophages. The most important protective antibodies include those which inactivate soluble toxic protein products of bacteria (antitoxins), facilitate phagocytosis and intracellular digestion of bacteria (opsonins), interact with the components of serum complement to damage the bacterial membrane with resultant bacteriolysis (lysins), or prevent proliferation of infectious virus (neutralizing antibodies). Alternatively, some antibodies may not be protective, and by "blocking" the adherence of, for example, neutralizing antibodies, they may actually depress the body's defenses.

Antigens react with antibody in the bloodstream and extracellular fluid and at mucosal surfaces. Antibodies cannot readily reach intracellular sites of infection as are found with viral replication. However, they are effective against many viral diseases (1) by interacting with virus before initial intracellular penetration occurs, and (2) by preventing locally replicating virus from disseminating from the site of entry to an important target organ, as in the spread of poliovirus from the gut to the central nervous system or of rabies from a puncture wound to peripheral neural tissue. Lymphocytes acting alone and antibody interacting with various types of effector (K–) cells may also recognize surface changes in virus-infected cells and destroy these infected "foreign" cells.

Passive Immunization

Immunization may be accomplished passively by administering either preformed immunoreactive serum or cells, or actively by presenting a suitable antigenic stimulus to the host's own immune system.

Antibody—either as whole serum or as fractionated, concentrated immune (gamma) globulin which is predominantly IgG—may be obtained from donors who have recovered from an infectious disease or have been immunized. These antibodies may provide immediate protection to an antibody-free individual. Passive immunization is thus useful for individuals who cannot form antibodies or for the normal host who might develop disease before active immunization could stimulate antibody production, which usually requires at least 7–10 days.

Antibody may be obtained from humans or animals, but animal sera are always less desirable since nonhuman proteins themselves give rise to an immune response which leads to rapid clearance of the protective molecules from the circulation of the recipient and may even result in clinical illness (serum sickness; see

Hazards of Passive Immunization, below). Thus, to obtain a similar protective effect, a much greater quantity of animal antiserum must be injected compared to human antiserum, eg, 3000 units of equine tetanus antitoxin versus 300 units of human tetanus immune globulin.

No antiserum of animal origin should be given without carefully inquiring about prior exposure or allergic response to any product of the specific animal source. Patients with an unrelated allergy are probably more prone to develop serum reactions. Whenever a foreign antiserum is administered, a syringe containing aqueous epinephrine 1:1000 should be available, and eye or scratch testing (see Chapter 32) should be followed by intracutaneous testing for hypersensitivity. If allergy is present by history or test and no alternative to serum therapy is possible, a patient may sometimes be given an essential medication to tolerance in repeated fractional doses of progressively increasing size. Simultaneous administration of antihistamines, corticosteroids, and even epinephrine may be necessary during this procedure of "desensitization," which may simply limit the allergic reactions to an acceptably small magnitude.

Persistence of certain human antibodies, eg, to varicella-zoster, is short-lived, and zoster immune globulin (ZIG) must therefore be prepared from the sera of convalescent zoster patients. By contrast, antibody to measles and hepatitis A is so ubiquitous in the population at large that normal serum globulin (ISG) will usually prevent or modify clinical illness with these infections if given early in the incubation period. Table 43–2 lists antisera generally available for passive immunization at present.

In the preantibiotic era, passive immunization was administered with some success as therapy for pneumococcal or *Haemophilus* infection. The need to identify the infecting serotype and obtain the appropriate type-specific antiserum, the illness caused by injection of the foreign proteins, and the relatively poor therapeutic response led to the prompt abandonment of this unsatisfactory method of treatment as soon as effective antimicrobial chemotherapy became available. Today, serum therapy for established illness is largely limited to the administration of antivenins and of botulinus, tetanus, and diphtheria antitoxins to block attachment of yet unbound toxin.

In the absence of demonstrably low serum IgG or (rarely) specific antibody deficiencies, the administration of normal immune human serum globulin (ISG) is of no value in the prevention of recurrent infections.

Passive Transfer of Cellular Immunity

Antibodies produced following some infections, particularly those due to mycobacteria, fungi, and many viruses, fail to protect against infection. Rather, interaction of immune lymphocytes and macrophages largely determines recovery from these illnesses. Attempts have been made to transmit this cell-mediated immunity, eg, to vaccinia virus in the progressively infected, immunologically incompetent host; to *Coccidioides immitis* in the patient with disseminated coccidioidomycosis; and to *Mycobacterium leprae* in lepromatous leprosy (see Chapter 37). Whole blood, leukocyte-rich buffy coat, and leukocyte-derived "transfer factor" (TF) have been utilized. The value of this type of therapy is uncertain, and these procedures are still experimental (see Chapter 44).

Hazards of Passive Immunization

Illness may arise from a single injection of foreign serum but more commonly occurs in patients who have previously been injected with proteins from the same or a related species. Reactions range in severity from acute anaphylaxis with hives, back pain, dyspnea, cardiovascular collapse, and even death to serum sickness arising hours to weeks following treatment. Typical manifestations of serum sickness include adenopathy, urticaria, arthritis, and fever. Demyelinating encephalopathy has been reported. Rarely, the administration of human γ-globulin is attended by similar allergic reactions, particularly in patients who are congenitally deficient in one or more immunoglobulins but still capable of mounting an immune response. Hepatitis A, B, or "C" (non-A, non-B) may be transmitted by whole human plasma or serum, but purified immune (gamma) globulin is free of hepatitis.

Note: Great care must be exercised in administering gamma globulin to avoid accidental intravenous injection. Currently, nearly all human and animal γ-globulin preparations are given by the intramuscular route. They all contain high-molecular-weight aggregated IgG, intravenous administration of which will frequently result in moderate to severe anaphylactic reactions with possible vasomotor collapse and death.

The administration of intact lymphocytes to promote cell-mediated immunity is also hazardous if the recipient is too immunologically depressed to prevent implantation of incompatible donor cells. The engrafted donor cells may "reject" the recipient by a GVH reaction, producing rash, pancytopenia, fever, diarrhea, hepatosplenomegaly, and death (see Chapter 31).

Active Immunization

Primary active immunity develops more slowly than the incubation period of most infections and must therefore be induced prior to exposure to the etiologic agent. One exception is vaccinia-induced immunity to smallpox, which takes only 10 days as opposed to the 14-day incubation period of the virulent infection. By contrast, "booster" reimmunization in the previously immune individual provides a rapid secondary (anamnestic) increase in serum antibody which outpaces the development—to give one example—of tetanus from a contaminated wound.

Active immunization may be achieved with either living or dead materials. Nonviable antigens usually are either structural components of the infecting organism which induce antibodies that prevent infection, or detoxified bacterial products (toxoids) which stimu-

Table 43–2. Materials available for passive immunization.

Disease	Product	Dosage	Comments
Black widow spider bite	Black widow spider antivenin, equine	1 vial IM or IV.	A second dose may be given if symptoms do not subside in 3 hours.
Botulism	ABE polyvalent antitoxin, equine	1 vial IV and 1 vial IM; repeat after 2–4 hours if symptoms worsen, and after 12–24 hours.	Available from CDC.* 20% incidence of serum reactions. Only type E antitoxin has been shown to affect outcome of illness. Prophylaxis is not routinely recommended but may be given to asymptomatic exposed persons.
Diphtheria	Diphtheria antitoxin, equine	20,000–120,000 units IM depending on severity and duration of illness.	Active immunization and (perhaps) erythromycin prophylaxis should be given to nonimmune contacts of active cases rather than antitoxin prophylaxis. Contacts should be observed for signs of illness so that antitoxin may be administered if needed.
Gas gangrene	Gas gangrene antitoxin, polyvalent, equine		Clinically ineffective. May not be available.
Hepatitis A ("infectious")	Immune serum globulin, human	0.02 mL/kg IM as soon as possible after exposure up to 6 weeks. A protective effect lasts about 2 months.	Modifies but does not prevent infection. Recommended for household contacts and other contacts of similar intensity. Not office or school contacts unless an epidemic appears to be in progress. Also recommended for travel to endemic areas.
		For chronic exposure, a dose of 0.1 mL/kg is recommended every 6 months.	Personnel of mental institutions, facilities for retarded children, and prisons appear to be at chronic risk of acquiring hepatitis A, as are those who work with nonhuman primates.
Hepatitis B ("serum")	Hepatitis B immune globulin, human	0.06 mL/kg IM as soon as possible after exposure, preferably within 7 days. A second injection should be given 25–30 days after exposure.	Administer to nonimmune individuals as postexposure prophylaxis following either parenteral exposure to or direct mucous membrane contact with HBsAg-positive materials. Should not be given to persons already demonstrating anti-HBsAg antibody. Administration of various live virus vaccines should be delayed for at least a couple of months after this concentrated immune globulin has been given. Some experts also advise administration of a single dose of 0.13 mL/kg to newborns of mothers who develop hepatitis B in the third trimester and who are seropositive at the time of delivery.
Hypogammaglobulinemia	Immune serum globulin, human	0.6 mL/kg IM every 3–4 weeks.	Give double dose at onset of therapy. ISG is of no value in the prevention of frequent respiratory infections in the absence of demonstrable hypogammaglobulinemia.
Measles	Immune serum globulin, human	0.25 mL/kg IM as soon as possible after exposure. This dose may be ineffective in immunoincompetent patients, who should receive 20–30 mL.	Live measles vaccine will usually prevent natural infection if given within 48 hours following exposure. If ISG is administered, delay immunization with live virus for 3 months. Do not vaccinate infants under age 15 months.
Mumps	Mumps immune globulin, human	1.5 mL IM for child; 4.5 mL for ≥ 12 years old.	Efficacy doubtful. Possibly useful in nonimmune boys to prevent orchitis, which occurs in up to 20% of cases but rarely causes sterility. Larger doses may be more effective if prophylaxis is delayed.
Pertussis	Pertussis immune globulin, human	1.5 mL IM.	Efficacy doubtful. May also be given for treatment, 1.25 mL IM, with repeat dose 24–48 hours later.
Rabies	Rabies immune globulin, human. (Equine antirabies serum may be available but is much less desirable.)	20 IU/kg, 50% of which is infiltrated locally at the wound site, and the remainder given IM. (See also rabies vaccine in Table 43–3.)	Give as soon as possible after exposure. Recommended for all bite or scratch exposure to carnivores, especially bat, skunk, fox, coyote, or raccoon, despite animal's apparent health, if the brain cannot be immediately examined and found rabies-free. Give also even for abrasion exposure to known or suspected rabid animals as well as for bite (skin penetration by teeth) of escaped dogs and cats whose health cannot be determined. Not recommended for individuals with demonstrated antibody response from preexposure prophylaxis.

*Center for Disease Control—Telephone: 404-329-3311 (main switchboard, day) or 404-329-3644 (night).

Note: Passive immunotherapy or immunoprophylaxis should always be administered as soon as possible after exposure to the offending agent. Immune antisera and globulin are always given intramuscularly unless otherwise noted. Always question carefully and test for hypersensitivity before administering animal sera.

Table 43–2 (cont'd). Materials available for passive immunization.

Disease	Product	Dosage	Comments
Rh isoimmunization (erythroblastosis fetalis)	Rh_0 (D) immune globulin, human	1 dose IM within 72 hours of abortion, amniocentesis, obstetric delivery of an Rh-positive infant, or transfusion of Rh-positive blood in an Rh_0 (D)-negative female.	For nonimmune females only. May be effective at much greater postexposure interval. Give even if more than 72 hours have elapsed. One vial contains 300 μg antibody and can reliably inhibit the immune response to a fetomaternal bleed of 7.5–8 mL as estimated by the Betke-Kleihauer smear technic.
Snakebite	Coral snake antivenin, equine Crotalid antivenin, polyvalent, equine	At least 3–5 vials IV.	Dose should be sufficient to reverse symptoms of envenomation. Consider antitetanus measures as well.
Tetanus	Tetanus immune globulin, human. (Bovine and equine antitoxins may be available but are not recommended. They are used at 10 times the dose of tetanus immune globulin.)	Prophylaxis: 250–500 units IM. Therapy: 3000–6000 units IM.	Give in separate syringe at separate site from simultaneously administered toxoid. Recommended only for major or contaminated wounds in individuals who have had fewer than 2 doses of toxoid at any time in the past (fewer than 3 doses if wound is more than 24 hours old). (See tetanus toxoid in Table 43–3.)
Vaccinia	Vaccinia immune globulin (VIG), human. (Available from CDC.*)	Prophylaxis: 0.3 mL/kg IM. Therapy: 0.6 mL/kg IM. VIG may be repeated as necessary for treatment and at intervals of 1 week for prophylaxis.	Give at a different site if used to prevent dissemination in a patient with skin disease who must undergo vaccination. May prevent or modify smallpox if given within 24 hours of exposure. May be useful in treatment of vaccinia of the eye, eczema vaccinatum, generalized vaccinia and vaccinia necrosum, and in the prevention of such complications in exposed patients with skin disorders such as eczema, burns, or impetigo. VIG in prophylactic dosage is also recommended for the pregnant woman who must be vaccinated to prevent fetal vaccinia.
Varicella	Varicella-zoster immune globulin (VZIG), human, or zoster immune globulin (ZIG), human	3–5 mL IM within 96 hours of exposure.	Available† for nonimmune leukemic, lymphomatous, immunosuppressed, or other immunoincompetent children under 15 years of age and with household, hospital (same 2- or 4-bed room or adjacent beds in large ward), or playmate (> 1 hour play indoors) contact with a known case of varicella-zoster, and for neonates whose mothers have developed varicella within 4 days before or 48 hours after delivery. VZIG and ZIG modify natural disease but may not prevent the development of immunity. Convalescent plasma collected 1–5 weeks after onset of varicella or zoster may be available at local blood banks and is also effective at 7–10 mL/kg IV. If neither VZIG, ZIG, nor convalescent plasma is available, normal immune serum globulin, 0.6–1.2 mL/kg IM, may modify the illness.

*Center for Disease Control—Telephone: 404-329-3311 (main switchboard, day) or 404-329-3644 (night).
†Contact Division of Clinical Microbiology, Sidney Farber Cancer Institute, Boston. Telephone 617-732-3121.
Note: Passive immunotherapy or immunoprophylaxis should always be administered as soon as possible after exposure to the offending agent. Immune antisera and globulin are always given intramuscularly unless otherwise noted. Always question carefully and test for hypersensitivity before administering animal sera.

late antitoxins that prevent illness without directly inhibiting the pathogen. Although tetanus toxoid provides a particularly long-lasting immunity of at least 10 years' duration, most nonliving vaccines provide protection for only a limited time. Repeated injections are needed to maintain even a moderate level of protection against plague, cholera, and typhoid fever. Not even natural infection always results in durable immunity. Examples include repeated, although perhaps milder, attacks of illness with *Mycoplasma pneumoniae* and respiratory syncytial virus as well as cholera. One of the most interesting experimental prospects for active immunization arises from the recent discovery of cross-reactivity of nonpathogenic bacteria with poorly immunogenic pathogens. Infants, particularly those under 6 months of age, do not reliably develop protective antibody responses to the polysaccharide antigens of *Haemophilus*, meningococcus, and pneumococcus, all important causes of severe illness in this age group. To some extent, this poor response may be overcome by multiple injections. The discovery that cross-reactive protective antibody may be induced by nonpathogenic serotypes of *E coli* and viridans streptococci has opened up the prospect of immunizing this

population by colonizing their intestinal and respiratory tracts with carefully selected saprophytic immunizing strains of these antigenic "relatives."

The route of immunization may be an important determinant of successful vaccination, particularly if nonreplicating immunogens are employed. Thus, immunization intranasally or by aerosol often appears to be more successful than parenteral injection against viral or bacterial challenges to the respiratory tree.

Active immunization with living agents is generally preferable to immunization with killed vaccines because of a superior and long-lived immune response. A single dose of a live, attenuated virus vaccine often suffices for reliable immunization. Multiple immunizations are recommended for polio in case intercurrent enteroviral infection or interference among the 3 simultaneously administered virus types in the trivalent vaccine prevents completely successful primary immunization. The durability of immunity to many viral infections is unexplained and may include repeated natural reexposure to new cases in the community, the unusually large antigenic stimulus which infection with a living agent provides, or other mechanisms such as the persistence of latent virus.

All immunizing materials—but live agents particularly—must be properly stored to retain effectiveness. Serious failures of smallpox and measles immunization have resulted from inadequate refrigeration prior to use. Agents presently licensed for active immunization are listed in Table 43–3.

Hazards of Active Immunization

Active immunization may cause fever, malaise, and soreness at injection sites. Some reactions are relatively specific for the immunizing agent, such as arthralgia/arthritis following rubella vaccine or convulsions following pertussis vaccine, but are much less frequent and less severe than those accompanying unmodified natural illness. Reactions known to be associated with a particular product are described in the manufacturer's package insert, the *Physicians' Desk Reference*, and standard texts.

Repeated immunization, particularly with diphtheria and tetanus toxoids, may result in increasingly severe local reactions. Diphtheria antigen in adult-type combined diphtheria-tetanus toxoid (Td) is therefore 5- to 10-fold less than in childhood DTP, and a lower frequency of booster immunization for tetanus is now recommended than in the past. Although experimentally hyperimmunized animals display a variety of adverse effects, including amyloidosis and malignancy, and immunization has been suspected of precipitating systemic lupus erythematosus in humans, follow-up of intensively immunized individuals over a 15-year period has not shown any clinical sequelae. Antibodies to certain bacteria reportedly cross-react with mammalian tissues, suggesting the potential hazard of autoimmune disease following extensive immunization, but the clinical significance of such experimental observations is unknown.

The careful monitoring system established during the 1976 "swine flu" immunization program revealed a 5-fold increase in postimmunization Guillain-Barré syndrome in comparison with unvaccinated controls. This complication arises within 10 weeks of immunization and has resulted in a 5% mortality rate, with another 5–10% of patients displaying residual weakness. The rarity of this complication (one case per 85,000) would not permit recognition in field trials or in the absence of a surveillance program and demonstrates the difficulty in accurately assessing the risks of immunization.

Allergic reactions may occur on exposure to egg protein or antibiotics in viral vaccine cell cultures. The quantity of irrelevant antigen in a vaccine is usually insufficient to elicit a response in the allergic individual, but a patient with intense allergy to a vaccine component may be given vaccine from a different source, if available. Improvements in antigenicity and better purification procedures in vaccine production decrease the amount and number of foreign substances injected and result in fewer side-effects.

Unique Hazards of Live Vaccines

Live vaccines should *not* be given to a pregnant woman because of their potential effect upon the fetus. Live vaccines, furthermore, can cause serious or even fatal illness in an immunologically incompetent host. They should not be given to patients receiving corticosteroids, alkylating drugs, and other immunosuppressive agents, nor to individuals who exhibit congenital or acquired defects in cell-mediated immunity, as seen in severe combined immunodeficiency disease or Hodgkin's disease. Patients with pure hypogammaglobulinemia but no defect in cell-mediated immunity usually tolerate viral infections and vaccines well but have a 10,000-fold excess of paralytic complications over the usual one case per million vaccinees, perhaps because of the frequent reversion of attenuated polio strains to virulence in the intestinal tract.

Even if not administered to immunoincompetent hosts, live vaccines may result in mild and, rarely, severe disease.

The early measles vaccines caused high fever and rash in a significant proportion of recipients. Subacute sclerosing panencephalitis, a rare complication of natural infection, has occurred following administration of live attenuated measles vaccine (see Chapter 39), but the rate of perhaps one case per million vaccinees is one-tenth to one-fifth the rate following natural measles.

Because passage through the human intestinal tract occasionally results in reversion of oral attenuated poliovirus vaccine (particularly type III) to neurovirulence, paralytic illness has occurred in recipients or their nonimmune contacts, especially adults. The success of live polio vaccines in preventing widespread natural infection has resulted in the paradox that the vaccine itself now causes most of the few cases of paralytic poliomyelitis seen each year in the USA. This

fact and the apparent success of a few countries in abolishing polio by the use of inactivated vaccine alone has reopened the question of replacing live (Sabin) with killed (Salk) vaccine some 15 years after the live vaccine displaced the killed virus on grounds of greater potency, ease of administration, and the advantages of "intestinal" immunity.

Vaccinia is not virulent for normal humans at its usual site of administration in the skin but may cause severe local illness if accidentally administered to a child with eczema or if rubbed into the eye.

Live vaccines may contain undetected and undesirable passengers. Epidemic hepatitis has resulted from vaccinia and yellow fever vaccines containing human serum. More recently, millions of people received SV40, a simian papovavirus, along with inactivated poliovirus vaccine prepared in monkey kidney tissue culture. It is disconcerting that a virus closely related to SV40 has been isolated from the brain of patients with the lethal degenerative disease progressive multifocal leukoencephalopathy although there is no known history of polio immunization in these cases. An increased incidence of malignancy in the children of mothers who received inactivated polio vaccine during pregnancy has, however, been suggested in 2 studies. The true extent of risk can only be established by elaborate prospective studies. SV40 can now be detected and excluded from human viral vaccines, but it is possible that presently undetected agents might be transmitted to humans with uncertain consequences, particularly by vaccines grown in nonhuman cell lines. Bacteriophages and, probably, bacterial endotoxins have also been shown to contaminate live virus vaccines, although without known hazard thus far.

Live viral vaccines probably do not interfere with tuberculin skin testing, although they depress some measurements of lymphocyte function.

Legal Liability for Untoward Reactions

It is the physician's responsibility to inform the patient of the risk of immunization and to employ vaccines and antisera in an appropriate manner. Certain of the risks described above are, however, currently unavoidable; on balance, the patient is better off for accepting them.

Manufacturers should be held legally accountable for failure to adhere to known production safeguards. However, in the present litigious atmosphere in the USA, the filing of large liability claims by the statistically inevitable victims of good public health practice could lead manufacturers to abandon efforts to develop and produce low-profit but medically valuable therapeutic agents, and if this happens, society as a whole will suffer. "Strict product liability" (liability without fault) may be an inappropriate legal standard in therapeutics; a policy that liability does not attach if the article could not have been regarded as defective in the light of the stage of scientific and technologic development when it was sold may more appropriately govern manufacturers' responsibilities for these products, whose use and sale are subject to careful review and approval by government bodies such as the Surgeon General's Advisory Committee on Immunization Practices and the Food & Drug Administration.

The cost of unpredictable untoward reactions not involving substandard manufacturing practices should logically be borne by the same public that reaps the benefits of control of disease (eg, paralytic poliomyelitis) and could be met through a national compensation scheme of the type recently established in the United Kingdom and Japan to cover vaccine-related injuries incurred during immunization under the National Health Service.

Nonspecific Active Immunization

Immunization with vaccinia has been employed in attempts to nonspecifically improve the immune response and thereby decrease the frequency of recurrences of herpes labialis (cold sores). Careful evaluation has shown that this practice is ineffective—and indeed has occasionally resulted in severe illness due to uncontrolled spread of vaccinia in a patient with unsuspected immunoincompetence.

Under some circumstances, specific activation of cell-mediated immunity may lead to enhanced nonspecific ability of "activated" macrophages to deal with other antigens. Such an interaction has been demonstrated experimentally for tuberculosis, *Salmonella, Brucella, Listeria,* and *Toxoplasma* infection of animals. The apparent effectiveness of BCG immunization in the prevention of leprosy may be related to this phenomenon as well as to an antigenic similarity between *Mycobacterium tuberculosis* and *Mycobacterium leprae*. The possibility that nonspecific stimulation of the immune system with *Bordetella pertussis, Corynebacterium parvum (Propionibacterium acnes),* endotoxins, or mycobacterial products can help the body to reject tumor cells is now being studied (see Chapters 23 and 44).

Combined Passive-Active Immunization

Passive immunization has been combined with active immunization to minimize untoward effects of certain active immunizing agents. Low-dose gamma globulin decreased the side-effects of the early attenuated measles vaccines, leading to greater patient acceptance. (Newer "further attenuated" vaccine strains no longer require the modifying effects of gamma globulin.) Similarly, vaccinia immune globulin decreases the likelihood of eczema vaccinatum if an eczematous patient must be vaccinated for travel to the (vanishing) smallpox-endemic area. Passive and active immunization are often simultaneously undertaken to provide both immediate but transient and slowly developing, durable protection against rabies or tetanus. The immune response to the active agent may or may not be impaired by gamma globulin if the injections are given at separate sites. Tetanus toxoid plus tetanus immune globulin may give a response superior to that generated by the toxoid alone, but after antiserum has been given for rabies, the course of

Table 43–3. Materials available for active immunization.*

Disease	Product (Source)	Type of Agent	Route of Administration	Primary Immunization	Duration of Effect	Comments
Cholera	Cholera vaccine	Killed bacteria	Subcut, IM, intradermal	2 doses 1 week or more apart.	6 months†	50% protective; International Certificate may be required for travel.
Diphtheria	DTP, DT (adsorbed) for child under 6; Td (adsorbed) for all others	Toxoid	IM	3 doses 4 weeks or more apart, with an additional dose 1 year later for a child under 6. (Can be given at the same time as polio vaccine if doses at least 8 weeks apart.)	10 years‡	Use DT if convulsions follow use of DTP. Give school children and adults third dose 6–12 months after second.
Influenza	Influenza virus vaccine, monovalent or bivalent (chick embryo). Composition of the vaccine is varied depending upon epidemiologic circumstances.	Killed whole or split virus A and/or B	IM	1 dose. (Two doses 4 weeks or more apart are preferable when a major new antigenic component is first incorporated into the vaccine. Two doses of the split virus products should be used in persons under 26 years because of a lower incidence of side-effects.)	1 year‡	Give immunization by November. Recommended annually for patients with cardiorespiratory disease, diabetes, other chronic diseases, and the elderly. Patients receiving chemotherapy for malignant disease are likely to respond better if immunized between courses of treatment.
Measles§	Measles virus vaccine, live attenuated (chick embryo)	Live virus	Subcut	1 dose at age 15 months.	Permanent	Reimmunize if given before 15 months of age; may prevent natural disease if given less than 48 hours after exposure.
Meningococcus	Meningococcal polysaccharide vaccine, group A or group C	Polysaccharide	Subcut	1 dose. Since primary antibody response requires at least 5 days, antibiotic prophylaxis with rifampin (600 mg or 10 mg/kg every 12 h for 4 doses) should be given to household contacts.	?Permanent	Recommended in epidemic situations, for use by the military to prevent outbreaks in recruits, and possibly as an adjunct to antibiotic prophylaxis in preventing secondary cases in family contacts. Not reliably effective in infants. A combination A-C vaccine is also available.
Mumps§	Mumps virus vaccine, live (chick embryo)	Live virus	Subcut	1 dose.	Permanent	Reimmunize if given before 1 year of age.
Pertussis	DTP	Killed bacteria	IM	As for DTP.	See‡	Not generally recommended after age 6.
Plague	Plague vaccine	Killed bacteria	IM	3 doses 4 weeks or more apart.	6 months‡	Recommended only for occupational exposure and not for residents of endemic area in the southwest USA.
Pneumococcus	Pneumococcal polysaccharide vaccine, polyvalent.	Polysaccharide	Subcut, IM	0.5 mL.	Uncertain—probably at least 5 years	Recommended for patients with cardiorespiratory disease or other chronic illness, for adults over 50, for patients with sickle cell disease, and for others with functional, congenital, or post-surgical asplenia. Only the 14 most common serotypes are represented in the vaccine. Infants respond unreliably.
Poliomyelitis	Poliovirus vaccine, live, oral, trivalent (monkey kidney, human diploid).	Live virus types I, II, III	Oral	2 doses 6–8 weeks or more apart, followed by a third dose 8–12 months later. (Can	Permanent	Recommended for adults only if at increased risk by travel to epidemic or highly endemic areas or occupational contact. In-

						liably.
Poliomyelitis	Poliovirus vaccine, live, oral, trivalent (monkey kidney, human diploid).	Live virus types I, II, III	Oral	2 doses 6–8 weeks or more apart, followed by a third dose 8–12 months later. (Can be given at the same time as primary DTP immunization.) A fourth dose before entering school is recommended for children immunized in the first 1–2 years of life.	Permanent	Recommended for adults only if at increased risk by travel to epidemic or highly endemic areas or occupational contact. Individuals who have completed a primary series may take a single booster dose if the risk of exposure is high.
	Poliomyelitis vaccine	Killed virus types I, II, and III	IM	3 doses 1–2 months apart, followed by a fourth dose 6–12 months later and a fifth dose before entering school.‡	2–5 years, perhaps longer	Killed virus vaccines are licensed but not readily available and are no longer recommended except for immunologically deficient patients or possibly for unimmunized adults who are at risk of exposure to poliomyelitis by reason of travel or immunization of their children.
Rabies	Rabies vaccine (duck embryo). (Vaccine derived from rabbit neural tissue may still be available but is undesirable because of the higher rate of neurologic side-reactions.) An experimental human diploid vaccine is available through state health departments for postexposure immunization of patients with demonstrated allergy to duck embryo vaccine, as a booster for those who have received the full course of rabies immune globulin and duck embryo vaccine and have failed to develop antibody titers ≥ 1:8, and for those who have been bitten by an animal proved to be rabid.	Killed virus	Subcut	**Preexposure:** 2 doses 1 month apart followed by a third dose 6–7 months later **or** 3 doses 1 week apart, followed by a fourth dose 3 months later. **Postexposure:** Always give rabies immune globulin as well. (See Table 43–2.) If not previously immunized, give a total of 23 doses. Give 2 injections per day for the first 7 days, then 7 daily doses, and boosters on days 24 and 34 following start of treatment. Alternatively, give 21 daily doses and boosters on days 24 and 34. *If previously immunized and an antibody response demonstrated,* do not give serum therapy. For nonbite exposure, give 1 booster dose. For the bite of a rabid animal, give 5 daily boosters followed by 1 dose on day 25. If an antibody response was not previously demonstrated, treat as unimmunized.	2 years‡	Preexposure immunization only for occupational or avocational risk or residence in hyperendemic area. Antibody response should be measured 3–4 weeks after last injection to ensure successful immunization, and repeat injection should be given if no response. For animal bite, consider antitetanus measures as well. Wounds should be copiously swabbed and flushed with soap and water. (See Table 43–2 regarding use of hyperimmune serum or immune globulin.)
Rubella§	Rubella virus vaccine, live (human diploid)	Live virus	Subcut	1 dose	Permanent	Give after 15 months of age. Do not give during pregnancy. Women must prevent pregnancy for 3 months after immunization.

*Dosages for the specific product, including variations for age, are best obtained from the manufacturer's package insert. Immunizations should be given by the route suggested for the product.
†Revaccination interval required by international regulations.
‡A single dose is a sufficient booster at any time after the effective duration of primary immunization has passed. A need for boosters after age 18 is uncertain.
§Combination vaccines available.

Table 43–3 (cont'd). Materials available for active immunization.*

Disease	Product (Source)	Type of Agent	Route of Administration	Primary Immunization	Duration of Effect	Comments
Smallpox	Smallpox vaccine (calf lymph, chick embryo)	Live vaccinia virus	Intradermal	1 dose.	3 years†	Not recommended except where certificate is required for travel. Revaccinate if no jennerian vesicle at 6–8 days postvaccination. Do not vaccinate if child or contacts have eczema or acute or chronic skin disease. If patients with skin disease must be vaccinated or exposed to a vaccinated household contact, they should receive vaccinia immune globulin. (See Table 43–2.)
Tetanus	DTP, DT (adsorbed(for children under age 6; Td, T (adsorbed) for all others	Toxoid	IM	3 doses 4 weeks or more apart.	10 years‡**	Give school children and adults a third dose 6–12 months after second. (See Table 43–2 regarding use of hyperimmune globulin.)
Tuberculosis	BCG vaccine	Live attenuated *Mycobacterium bovis*	Intradermal, subcut	1 dose.	?Permanent††	Recommended in USA only for PPD-negative contacts of ineffectively treated or persistently untreated cases and for other unusually high-risk groups.
Typhoid	Typhoid vaccine	Killed bacteria	Subcut	2 doses 4 weeks or more apart or 3 doses 1 week apart (less desirable).	3 years‡	70% protective. Recommended only for exposure from travel, epidemic, or household carrier and not, eg, because of floods.
Typhus	Typhus vaccine (chick embryo)	Killed bacteria	Subcut	2 doses 4 weeks or more apart.	6–12 months‡	Recommended only for occupational exposure to louse-borne (epidemic) infection.
Yellow fever	Yellow fever vaccine (chick embryo)	Live virus	Subcut	1 dose.	10 years†	Certificate may be required for travel. Recommended for residence in or travel to endemic areas of Africa and South America.

*Dosages for the specific product, including variations for age, are best obtained from the manufacturer's package insert. Immunizations should be given by the route suggested for the product.
†Revaccination interval required by international regulations.
‡A single dose is a sufficient booster at any time after the effective duration of primary immunization has passed.
**For contaminated or severe wounds, give booster if more than 5 years have elapsed since full immunization or last booster.
††Test for PPD conversion 2 months later and reimmunize if there is no conversion.

immunization is usually extended to ensure an adequate response.

Anomalously Severe Disease in the Immunized Host

Immunization may not limit the spread of infection and may sometimes contribute to the pathogenesis of the disease. A child who has received killed measles virus vaccine (no longer recommended) may attain only a poorly protective level or type of serum antibody combined with a delayed hypersensitivity, which results in atypical and unusually severe rubeola upon exposure to wild virus or in an erythematous painful injection site, fever, and eye pain if reimmunization with live vaccine is performed. A poorly antigenic experimental respiratory syncytial virus vaccine increased the intensity of subsequent natural illness in infant recipients. Mice congenitally infected with lymphocytic choriomeningitis virus are clinically well until they begin to produce antibody to the virus; they then develop a fatal disorder resulting from the deposition of antigen-antibody complexes in the central nervous system and kidney. Similar poorly understood problems of intensified disease in immunized subjects have been noted with experimental trachoma and *Mycoplasma pneumoniae* vaccines.

The Decision to Immunize an Individual

Immunizing procedures are among the most effective and economical measures available for preservation and protection of health.

The decision to immunize a specific person against a specific pathogen is a complex judgment based upon an assessment of the risk of infection, the consequences of natural unmodified illness, the availability of a safe and effective immunogen, and the duration of its effect.

The organisms that cause diphtheria and tetanus are ubiquitous and the vaccines have few side-effects and are highly effective, but only the immunized individual is protected. Thus, immunization must be universal.

By contrast, a nonimmune individual who resides in a community which has been well immunized against poliovirus and who does not travel has little opportunity to encounter wild (virulent) virus. Here the immunity of the "herd" protects the unimmunized person since the intestinal tracts of recipients of oral poliovaccine fail to become colonized by or transmit wild virus. If, however, a substantial portion of the community is not immune, introduced wild virus can circulate and cause disease among the nonimmune group. Thus, focal outbreaks of poliomyelitis have occurred in religious communities objecting to immunization.

An intense debate has been in progress in Great Britain for the past few years over the relative risk of pertussis versus the occasional (1:10,000) neurologic complications of pertussis vaccination, an argument fueled by the discovery that the immunizing material in use prior to 1968 was poorly protective against prevalent serotypes of the infecting agent. The vigor of the opposing arguments is an illustration of the extent to which well-informed experts can disagree.

Smallpox vaccine is effective and usually safe, but the immunity it confers is of relatively short duration, declining after about 3 years. The last known case of naturally occurring smallpox was reported from Somalia in October 1977, and the risk from even the low rate of complications significantly exceeds the benefits of vaccination. Thus, vaccination against smallpox is no longer recommended.

Currently available rabies vaccines do rarely give rise to severe reactions. The risk of exposure is low, and preexposure immunization is thus reserved for travelers to hyperendemic areas or to persons with occupational hazard.

Cholera immunization offers only temporary and incomplete protection. It is of little use to travelers and should only be given where the risk of exposure is high or in fulfillment of local regulations.

Each immunologically distinct viral subtype requires a specific antigenic stimulus for effective protection. Immunization against adenovirus infection has not benefited civilian populations subject to many differing types of virus—in contrast to the demonstrated value of vaccine directed against a few epidemic adenovirus types in military recruits. Similarly, immunity to type A influenza virus is transient because of major mutations in surface chemistry of the virus every few years (antigenic shifts). These changes render previously developed vaccines obsolete and may prevent sufficient production, distribution, and utilization of new antigen in time to prevent epidemic spread of the altered strain. Major antigenic changes have been detected in visna virus recovered 1 year after experimental inoculation, suggesting a mechanism of persisting infection as well as a profound barrier to developing a successful vaccine. Antigenic variation may also be an important impediment to immunization against trypanosomes.

Age at Immunization

The natural history of a disease determines the age at which immunization is best undertaken. Pertussis, polio, and diphtheria often strike in infancy; immunization against these diseases is therefore begun shortly after birth. Serious consequences of pertussis are uncommon beyond early childhood, and pertussis vaccination is not usually recommended after 6 years of age. Since the major hazard of rubella is the congenital rubella syndrome, and since nearly half of congenital rubella occurs with the first pregnancy, it is very important to immunize as many females as possible prior to puberty. One thereby also avoids the theoretical hazard of vaccinating a pregnant female and endangering the fetus, although inadvertently immunized fetuses have thus far not been found to be damaged by their exposure to the attenuated virus.

The efficacy of immunization may also be age-related. Failure may occur because of the presence of

interfering antibodies or an undeveloped responsiveness of the immune system. Infants cannot be reliably protected with live measles, mumps, or rubella vaccines until maternally derived antibody has disappeared. Because of the reported failure of measles vaccination in a proportion of children immunized as late as 1 year of age, the age recommended for measles vaccine administration has recently been changed to 15 months, and some workers have made the same suggestion for rubella vaccine administration. Children (now teenagers) who were vaccinated at an earlier age in accordance with recommendations in effect at that time should be revaccinated. Infants frequently develop severe infections with *Haemophilus influenzae* type b, but injecting them with purified capsular polysaccharide has failed to reliably yield a good antibody response despite the excellent activity of the same antigen in older children and adults. Indeed, one study has shown that several children with early severe disease due to *H influenzae* did not develop active immunity and also failed to show a good antibody response to vaccine administered after 2 years of age. This failure to respond raises the question of a possible immune defect in the patients most in need of protection.

Simultaneous Immunization With Multiple Antigens

Simultaneous immunization with several antigenic stimuli might be expected to result in interference by the immune response to one antigen with the development of immunity to other antigens. Actually, the simultaneous inoculation of the nonliving antigens of diphtheria, tetanus, and pertussis gives a response equal to that seen with their separate injection; the endotoxic components of *Bordetella pertussis* may even act as an adjuvant, providing a superior immune response against the additional antigens.

Similarly, the single injection of a mixture of live, attenuated measles, rubella, and mumps viruses or the simultaneous administration of live measles, smallpox, and yellow fever vaccines gives good responses to each component of the mixture. However, between 2 and 14 days following the administration of one live virus vaccine, there is a period of suboptimal response to a **subsequently injected** live virus vaccine. It is best to administer multiple immunizing agents according to a schedule which has been demonstrated to yield an effective response.

Recommendations for Childhood Immunization

A rational program of immunization against infectious diseases begins in childhood, when many of the most damaging and most preventable infections normally appear. Table 43–4 summarizes the current guidelines for immunization in childhood as compiled by the Expert Committee on Infectious Diseases of the American Academy of Pediatrics. The need for childhood immunization is actually increased since unimmunized individuals in a partially immune population will be less exposed to and will therefore develop later than they otherwise would such typically childhood diseases as measles and mumps. When these illnesses do occur in adolescence or adulthood, they are often much more severe than in childhood as well as being diagnostically bewildering to the physician unprepared for such illnesses in this age group. Epidemic measles is thus being reported in college students for the first time. The 1976 USA immunization survey disclosed immunization rates of 70%, 75%, 72%, and 78% for 5- to 9-year-olds against rubella, measles, polio, and DTP, respectively.

Immunization of Adults for Foreign Travel

National health authorities may require an International Certificate of Vaccination against smallpox, cholera, or yellow fever from travelers, usually depending upon the presence of these diseases in countries on their itinerary. Smallpox and cholera vaccinations may be given by any licensed physician. The certificate must be completed in all details and then validated with an approved stamp. Yellow fever vaccination may only be administered and the certificate validated at an officially designated center (these may be located by contacting the state or local health department). In addition to these legal requirements, all adults are advised to be adequately immunized against tetanus and diphtheria and to undergo additional immunizations (polio, typhoid, hepatitis A, plague, typhus) if visiting areas where the frequency of illness in the population or the level of sanitation increases the risk of infection. (Travelers to malaria-endemic areas should also be advised regarding chemoprophylaxis.) Information regarding individual agents may be found in Tables 43–2 and 43–3.

No special immunizations are generally recommended for persons traveling from the USA to Western Europe, Canada, or Australia. Detailed suggestions of

Table 43–4. Guidelines for routine immunization of normal infants and children.

Disease	Vaccine	Schedule of Doses				
		First	Second	Third	Fourth	Fifth
Diphtheria-tetanus-pertussis	DTP, adsorbed	2 months	4 months	6 months	1½ years	4–6 years*
Poliovirus I, II, and III	Oral trivalent	2 months	4 months	6 months†	1½ years	4–6 years
Measles-mumps-rubella	MMR or singly	15 months	...	...	...	...

*Adult-type combined tetanus-diphtheria toxoid (Td) is recommended at 10-year intervals thereafter.
†Optional in nonendemic areas.

the USPHS are given country-by-country in its Health Information for International Travel Supplement (see references).

Vaccines of Restricted Availability & Experimental Vaccines

A number of vaccines have been developed that are available for individuals at greatly increased occupational risk but not for the general public. Only a partial listing will be given here.

Adenovirus. Live attenuated oral vaccines have been developed for military use. These are directed against the 2 types of virus—types 4 and 7—that commonly cause severe epidemic disease in recruits. Experimental vaccines have been formulated against additional (civilian) serotypes.

Anthrax. A protein antigen extracted from culture filtrates can protect those who work with imported animal hides and hair and others with occupational exposure.

Arbovirus (various). Vaccines against certain agents causing equine encephalitis are available for persons working with the viruses.

Cholera. The poor immunity induced by commercially available whole-cell vaccines has led to the development of experimental vaccines directed against purified heat- and formalin-inactivated toxin. Oral immunization may be more effective than parenteral.

Cytomegalovirus. A live attenuated vaccine grown in a human diploid cell line has been shown to be immunogenic when given subcutaneously but not intranasally. The safety and efficacy of the vaccine, in view of the propensity of herpesviruses to cause latent infections which give rise to disease at the time of reactivation, remain to be demonstrated. It is noteworthy, however, that transplacental antibody does appear to protect a second congenitally infected infant of a chronically infected mother from clinical disease.

Dental caries. Animals are being immunized with enzymes extracted from cariogenic streptococci in an effort to block bacterial adhesion to the tooth surface and therefore prevent caries formation.

***E coli* enterotoxin.** Rats have been protected against heat-labile toxin following active immunization by the parenteral or oral route. Homologous protection against oral reinfection has also been demonstrated in human volunteers who have recovered from diarrheal illness.

Gonococci. Although experimental vaccines have been shown to produce antibody, the role of immunity in protecting against gonococcal infection is not known at this time. A number of differing gonococcal immunotypes have been identified, consistent with the clinical experience of multiple episodes of illness in an individual and suggesting that vaccine development will be difficult.

***Haemophilus influenzae* type b.** The major antigen, capsular polyribophosphate, does not induce protective antibody in infants. Oral immunization with cross-reactive *E coli* appears promising.

Hepatitis B. Formalinized virus is antigenic and protective in chimpanzees and is undergoing testing in humans. Preliminary results are encouraging. The technic of DNA sequencing is leading to information about the structure of various antigens that may lead to an even more effective nonliving immunogen.

Herpesvirus hominis. Formalinized vaccine has failed to yield protection in 2 separate human trials despite success in animal models. Immunosuppressed recipients of renal transplants, whose cell-mediated immunity is impaired, may develop severe herpetic disease despite very high levels of antibody.

Influenza. Live attenuated vaccines, including mutant strains that replicate poorly at deep body temperature, are being examined as potentially superior immunizing agents compared to currently licensed killed vaccines. Intranasal immunization with live virus is attractive as a means of improving the local barriers to initiating infection, but minor decreases in pulmonary function are detected from 1–3 weeks thereafter, and the hazard to subjects with damaged lungs has not been defined. Other approaches being examined include the use in Russia of orally administered live attenuated strains and the use of recombinant viruses containing only new viral neuraminidase antigens. The latter vaccine is less protective than a vaccine inducing antibody against the new viral hemagglutinin but permits colonization and active immunization by asymptomatic or clinically attenuated illness.

Legionella. Avirulent strains are readily produced on subculture and appear to be effective immunizing agents in guinea pigs.

Leprosy. Cutaneous sensitization to oil-free, killed *M leprae* has been successfully accomplished in guinea pigs, raising the possibility of human vaccination studies.

Lipopolysaccharide. Vaccines directed against the somatic O antigens of gram-negative bacteria are partially protective against infection with these organisms, eg, pertussis, cholera, plague, and typhoid vaccines. The antigenic heterogeneity of the many serotypes of different species has made a general "anti-O" vaccine impractical. Recent investigations of the structure of the endotoxic lipopolysaccharides of gram-negative species have revealed a common "core" antigen shared by nearly all species. Vaccines prepared from bacterial mutants which produce only core lipopolysaccharide can protect experimental animals against experimental infection with heterologous species, offering an exciting prospect for immunologic control of gram-negative sepsis, the commonest fatal nosocomial infection. Specific "anti-O" vaccines may decrease the extent of renal damage in ineradicable chronic urinary infections.

Malaria. Killed falciparum merozoites given in Freund's complete adjuvant have protected humans against challenge with *Plasmodium falciparum,* and these asexual erythrocyte forms of the parasite have now been successfully cultured in vitro.

Meningococcus. The protection-inducing antigen for group B is probably a type-specific protein, not a group-defining polysaccharide, as in groups A and

C. Vaccines are also under development for groups Y and W135. Because infants respond poorly to meningococcal and other polysaccharides, immunization by feeding cross-reactive *E coli* is also being considered.

Multiple sclerosis. Extracts of myelin basic protein, an extract of neural tissue, are being tested for their potential to absorb antibodies that would otherwise attack the patient's own nervous system.

Mycoplasma pneumoniae. Early killed vaccine may have caused more severe disease in the immunized host. Live, temperature-sensitive mutants which cannot multiply at the temperature of the lower respiratory tract induce protection against experimental challenge with more virulent strains. Experimental vaccination of animals has shown poor correlation of complement-fixing antibody and protection. Live vaccine is superior to inactivated vaccine, and the intranasal route of immunization is more effective than the subcutaneous. Since low levels of mycoplasmacidal antibody are found in a high proportion of children below the age of 5, and since repeat attacks of mycoplasmal pneumonia are well documented, it would appear that antibody is not protective against this infection or that immunity is particularly short-lived, making the long-term value of immunization uncertain. Experimental studies in mice suggest that persistence of intranasal immunity may be more important than serum antibody levels.

Pneumococcus. Temperature-sensitive noninvasive mutants capable of colonizing the upper airways are being studied as possible immunogens, as are antigenically related viridans streptococci.

Pseudomonas aeruginosa. Polyvalent vaccines can stimulate the development of protective opsonizing antibodies, but clinical usefulness in immunosuppressed, neutropenic patients most at risk from this organism has not been demonstrated. Vaccination may protect the patient with normal humoral immunity and normal white cell count against bacteremia from infected burns. Side reactions to immunization are frequent. Serotype-specific polysaccharide antigens are also being evaluated.

Respiratory syncytial (RS) virus. Recipients of killed vaccines developed more serious illness than unimmunized infants. Live attenuated and temperature-sensitive virus vaccines are being evaluated, as is parenteral administration of wild virus, which appears not to cause illness in young children while inducing neutralizing antibody.

Rhinovirus. Live and inactivated vaccines have been produced. Their use does not appear promising at present because of the multiplicity of serotypes that would be needed and because even natural immunity offers only partial protection.

Shigella. Live attenuated oral vaccines utilizing either noninvasive hybrid *E coli* modified to carry *Shigella* antigens or streptomycin-dependent shigellae are being evaluated. Lack of immunogenicity and reversion to virulence, respectively, have been problems in the development of these 2 vaccines.

***Streptococcus* group A.** Experimental vaccines can induce antibody but may not prevent colonization and possibly may even increase the likelihood of acute rheumatic fever. Hyperimmunized animals develop autoantibodies to smooth muscle, myocardium, albumin, and IgG.

***Streptococcus* group B.** The commonest agent of neonatal meningitis colonizes the female genital tract and causes disease in the absence of transplacentally shared maternal antibody directed against the type-specific antigens. Purified capsular polysaccharide antigen has been prepared from the type III organisms most commonly found in neonatal infection and is under investigation as an immunizing agent for the mother to ensure adequate antibody levels in the neonate at delivery. To avoid the possibility of immunologic paralysis of the fetus, it might be necessary to immunize women of childbearing age before pregnancy. However, protective antibody levels in the mother do not always result in protective levels in cord sera.

Typhoid. Live oral attenuated mutants provide superior protection and decrease enteric carriage of the infective organism.

Varicella. A live attenuated virus is probably effective in inducing antibody and preventing or modifying illness. However, the safety of a live virus vaccine remains to be conclusively demonstrated in the immunoincompetent patients most likely to develop life-threatening complications of wild virus infection. Small numbers of leukemic children and children with solid tumors have been immunized without complications and apparently protected against natural infection. The vaccine virus does not appear to spread readily to contacts.

IMMUNIZATION AGAINST NONINFECTIOUS DISEASES

Prevention of Rh Isoimmunization

Rh-negative females who have not already developed anti-Rh antibodies should receive Rh immune globulin within 72 hours after obstetric delivery, abortion, accidental transfusion with Rh-positive blood, and, probably, amniocentesis, especially if the needle passes through the placenta. This passive immunization suppresses the mother's normal immune response to any Rh-positive fetal cells that may enter her circulation, thus avoiding erythroblastosis fetalis in future Rh-positive fetuses. Even if more than 72 hours has elapsed after exposure, the globulin should be administered, since it will be effective in at least some cases. Three of 6 subjects were protected from the immunogenic effect of 1 mL of Rh-positive red cells given intravenously by 100 μg of anti-Rh globulin given 13 *days* later. Some workers have also suggested the administration of anti-Rh globulin to Rh-negative newborn female offspring of Rh-positive mothers to prevent possible sensitization from maternal-fetal transfusion (see Chapter 31).

A significant proportion of Rh isoimmunizations occur during pregnancy rather than at the time of delivery. Published studies suggest that this sensitization can be prevented by administration of anti-Rh globulin throughout pregnancy, despite the theoretical risks of the globulin crossing the placenta and causing erythroblastosis in the fetus.

Serum Therapy of Poisonous Bites

The toxicity of the bite of the black widow spider, the coral snake, and crotalid snakes (rattlesnakes and other pit vipers) may be lessened by the administration of commercially available antivenins.

Antisera for scorpion stings and rarer poisonous bites, especially of species foreign to North America, may also be available.

A central directory for information on use and availability of antivenins is maintained by the American Association of Zoological Parks and Aquariums at the Antivenin Index Center in Oklahoma City, OK 73126; (405) 271-5454. This service, which is available on a 24-hour basis, should be particularly useful in cases of snakebite by exotic species. The Center should be given the correct scientific name as well as the common name of the biting species; with this information, it can provide information about the availability and location of the nearest supply of antiserum as well as the names and emergency telephone numbers of persons able to supply the antisera and give expert advice.

• • •

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FDA panel backs Lyme disease vaccine

May 26, 1998
Web posted at: 11:18 p.m. EDT (0318 GMT)


The LYMErix vaccine

BETHESDA, Maryland (CNN) -- Government scientists cautiously recommended Tuesday that the first vaccine against Lyme disease be approved for sale in the United States. The vaccine, called LYMErix, requires three shots over a year's time and is about 80 percent effective.

The advisory panel for the Food and Drug Administration added several warnings to its approval of LYMErix: it should not be used by children under 16 or people with chronic arthritis, and no one should receive booster shots until the drug's maker, SmithKline Beecham, completes further study.

The FDA is not bound by the panel's recommendations but typically follows them.

Because Lyme disease is a serious threat in parts of the country, "the benefits are on the side of the vaccine in the short term," said Dr. Dixie Snider of the Centers for Disease Control and Prevention. "In the long term, we don't know."

El Niño could mean more ticks

Lyme disease is spread by tiny deer ticks, and 1998 could be a banner year for the insects.


Deer tick

Dr. Philip Baker of the National Institutes of Health told CNN, "We expect there might be an increase this year and perhaps the following year because of the large amount of rainfall we've had with El Niño."

Lyme disease can be cured with antibiotics if it's recognized and treated quickly, but the symptoms are often overlooked. Left untreated, it can severely damage the heart and nervous system and cause debilitating arthritis.

Symptoms include a bull's-eye shaped rash, fatigue, chills, fever and joint pain. Cases have occurred in 49 states but are most common in the Northeast and upper Midwest.

LYMErix is unlike typical vaccines that fight infection already inside the body. LYMErix creates antibodies that recognize an outer protein of the Lyme bacterium called Osp-A.

When the tick begins sucking a vaccinated person's blood, it would also ingest these antibodies, which would neutralize the Lyme germs before they enter the tick's victim.

Keep checking for ticks

In a study of 10,936 people in high-Lyme states, LYMErix proved 79 percent effective at preventing Lyme infections after the third dose.

But the third dose is given a full year after the first shot, and the vaccine is only 50 percent effective in that first year. Once people got the third shot, their level of protective antibodies increased tenfold.

So people still must check for ticks.

"There's going to have to be a lot of patient education. That dose you got before warm weather this year ... doesn't allow you to go play in the woods willy-nilly," said Dr. Robert Daum of the University of Chicago.

LYMErix's main side effects were soreness and swelling at the vaccine site, plus a few days of joint pain, fatigue and fever. SmithKline has begun studies to answer some of the panel's questions, including booster doses and the vaccine's effect in children, but most of the results will not be available in time for next year's tick season.

Reporter Louise Schiavone and The Associated Press contributed to this story.

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immuno biology 5

THE IMMUNE SYSTEM IN HEALTH AND DISEASE

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A-2 Routes of immunization.

The route by which antigen is administered affects both the magnitude and the type of response obtained. The most common routes by which antigen is introduced experimentally or as a vaccine into the body are injection into tissue by **subcutaneous** (s.c.) injection between the epidermis and dermal layers, or by **intradermal** (i.d.) injection, or **intramuscular** (i.m.) injection; by **intravenous** (i.v.) injection or transfusion directly into the bloodstream; into the gastrointestinal tract by **oral** administration; into the respiratory tract by **intranasal** (i.n.) administration or inhalation.

Antigens injected subcutaneously generally elicit the strongest responses, most probably because the antigen is taken up by Langerhans' cells and efficiently presented in local lymph nodes, and so this is the method most commonly used when the object of the experiment is to elicit specific antibodies or T cells against a given antigen. Antigens injected or transfused directly into the bloodstream tend to induce immune unresponsiveness or tolerance unless they bind to host cells or are in the form of aggregates that are readily taken up by antigen-presenting cells.

Antigen administration via the gastrointestinal tract is used mostly in the study of allergy. It has distinctive effects, frequently eliciting a local antibody response in the intestinal lamina propria, while producing a systemic state of tolerance that manifests as a diminished response to the same antigen if subsequently administered in immunogenic form elsewhere in the body. This 'split tolerance' may be important in avoiding allergy to antigens in food, as the local response prevents food antigens from entering the body, while the inhibition of systemic immunity helps to prevent the formation of IgE antibodies, which are the cause of such allergies (see Chapter 12).

Introduction of antigen into the respiratory tract is also used mainly in the study of allergy. Protein antigens that enter the body through the respiratory epithelium tend to elicit allergic responses, for reasons that are not clear.

A-3 Effects of antigen dose.

The magnitude of the immune response depends on the dose of immunogen administered. Below a certain threshold dose, most proteins do not elicit any immune response. Above the threshold dose, there is a gradual increase in the response as the dose of antigen is increased, until a broad plateau level is reached, followed by a decline at very high antigen doses (see Fig. A.1). As most infectious agents enter the body in small numbers, immune responses are generally elicited only by pathogens that multiply to a level sufficient to exceed the antigen dose threshold. The broad response optimum allows the system to respond to infectious agents across a wide range of doses. At very high antigen doses the immune response is inhibited, which may be important in maintaining tolerance to abundant self proteins such as plasma proteins. In general, secondary and subsequent immune responses occur at lower antigen doses and achieve higher plateau values, which is a sign of immunological memory. However, under some conditions, very low or very high doses of antigen may induce specific unresponsive states, known respectively as acquired **low-zone** or **high-zone tolerance**.

A-4 Adjuvants.

Most proteins are poorly immunogenic or nonimmunogenic when administered by themselves. Strong adaptive immune responses to protein antigens almost always require that the antigen be injected in a mixture known as an

adjuvant. An adjuvant is any substance that enhances the immunogenicity of substances mixed with it. Adjuvants differ from protein carriers in that they do not form stable linkages with the immunogen. Furthermore, adjuvants are needed primarily for initial immunizations, whereas carriers are required to elicit not only primary but also subsequent responses to haptens. Commonly used adjuvants are listed in Fig. A.4.

Adjuvants can enhance immunogenicity in two different ways. First, adjuvants convert soluble protein antigens into particulate material, which is more readily ingested by antigen-presenting cells such as macrophages. For example, the antigen can be adsorbed on particles of the adjuvant (such as alum), made particulate by emulsification in mineral oils, or incorporated into the colloidal particles of ISCOMs. This enhances immunogenicity somewhat, but such adjuvants are relatively weak unless they also contain bacteria or bacterial products. Such microbial constituents are the second means by which adjuvants enhance immunogenicity, and although their exact contribution to enhancing immunogenicity is unknown, they are clearly the more important component of an adjuvant. Microbial products may signal macrophages or dendritic cells to become more effective antigen-presenting cells (see Chapter 2). One of their effects is to induce the production of inflammatory cytokines and potent local inflammatory responses; this effect is probably intrinsic to their activity in enhancing responses, but precludes their use in humans.

Nevertheless, some human vaccines contain microbial antigens that can also act as effective adjuvants. For example, purified constituents of the bacterium *Bordetella pertussis*, which is the causal agent of whooping cough, are used as both antigen and adjuvant in the triplex DPT (diphtheria, pertussis, tetanus) vaccine against these diseases.

Adjuvants that enhance immune responses

Adjuvant name	Composition	Mechanism of action
Incomplete Freund's adjuvant	Oil-in-water emulsion	Delayed release of antigen; enhanced uptake by macrophages
Complete Freund's adjuvant	Oil-in-water emulsion with dead mycobacteria	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators in macrophages
Freund's adjuvant with MDP	Oil-in-water emulsion with muramyldipeptide (MDP), a constituent of mycobacteria	Similar to complete Freund's adjuvant
Alum (aluminum hydroxide)	Aluminum hydroxide gel	Delayed release of antigen; enhanced macrophage uptake
Alum plus *Bordetella pertussis*	Aluminum hydroxide gel with killed *B. pertussis*	Delayed release of antigen; enhanced uptake by macrophages; induction of co-stimulators
Immune stimulatory complexes (ISCOMs)	Matrix of Quil A containing viral proteins	Delivers antigen to cytosol; allows induction of cytotoxic T cells

Fig. A.4 Common adjuvants and their use. Adjuvants are mixed with the antigen and usually render it particulate, which helps to retain the antigen in the body and promotes uptake by macrophages. Most adjuvants include bacteria or bacterial components that stimulate macrophages, aiding in the induction of the immune response. ISCOMs (immune stimulatory complexes) are small micelles of the detergent Quil A; when viral proteins are placed in these micelles, they apparently fuse with the antigen-presenting cell, allowing the antigen to enter the cytosol. Thus, the antigen-presenting cell can stimulate a response to the viral protein, much as a virus infecting these cells would stimulate an anti-viral response.